5.2 Efficacy in Rheumatoid Arthritis

Seven studies, two pivotal and four supportive, and one open-label long-term safety study, were conducted in patients with RA to provide evidence for the efficacy of celecoxib for the treatment of signs and symptoms of RA (Table 14). The data presented in this section are primarily from the pivotal studies (022, 023), which were double-blind, placebo-controlled trials of 12 weeks duration with 200 or more patients per treatment. The four supportive controlled studies (012, 041, 062, and 071) are each summarized briefly.

Table 14. Summary of Celecoxib RA Studies

Study No. - Population	Duration	No. of Patients	Treatments
Pivotal Studies			
022 - RA flare	12 Weeks	1149	Celecoxib 100, 200, or 400 mg BID ; naproxen 500 mg BID; or placebo
023 - RA flare	12 Weeks	1103	Celecoxib 100, 200, or 400 mg BID ; naproxen 500 mg BID; or placebo
Supportive Controlled Studies			
012 - RA flare	4 weeks	330	Celecoxib 40, 200, or 400 mg BID or placebo
041 - Stable RA	24 weeks	655	Celecoxib 200 mg BID or diclofenac SR 75 mg BID
062 - OA or RA	12 weeks	537 (148 RA)	Celecoxib 200 mg or naproxen 500 mg BID
071 - OA or RA	12 weeks	1099 (287 RA)	Celecoxib 200 mg BID, diclofenac 75 mg BID, or ibuprofen 800 mg TID
Open-Label Study			
024 - OA or RA	1-2 years	4499 (1945 RA)	Celecoxib 200-400 mg BID for RA

5.2.1 Pivotal RA Efficacy Studies: Studies 022 and 023

5.2.1.1 Population and Design

The two pivotal studies (Studies 022 and 023) were randomized, multicenter, double-blind, active- and placebo-controlled comparison studies of the efficacy and safety of celecoxib 100 mg BID, 200 mg BID, and 400 mg BID and naproxen 500 mg BID in patients with RA.

Study patients were required to have RA in a flare state at Baseline subsequent to discontinuation of NSAID therapy. An RA flare was demonstrated if the Physician's Global Assessment of Arthritic Condition and the Patient's Global Assessment of Arthritic Condition were "fair," "poor," or "very poor" at the Baseline Visit and if a

comparison of the Screening arthritis assessments and the Baseline arthritis assessments met criteria 1 and 2 described below plus either criterion 3 or 4:

1. A minimum of six tender joints at the Baseline Arthritis Assessment AND an increase of at least two tender or painful joints (or 20% increase in the number of tender/painful joints, whichever was greater) at the Baseline Visit compared to the Screening Visit.
2. A minimum of three swollen joints at the Baseline Arthritis Assessment AND an increase of at least two swollen joints (or 20% increase in the number of swollen joints, whichever was greater) at the Baseline Visit compared to the Screening Visit.
3. A minimum of 45 minutes of morning stiffness at the Baseline Arthritis Assessment AND an increase in the duration of morning stiffness of at least 15 minutes at the Baseline Visit compared to the Screening Visit.
4. Patient's Assessment of Arthritis Pain measurement of at least 40 mm (on the VAS) at the Baseline Arthritis Assessment AND an increase of 10 mm (or 20% increase, whichever was greater) at the Baseline Visit compared to the Screening Visit.

Patients in these studies may have been on disease-modifying anti-rheumatic drug (DMARD) therapy but could not have begun taking any of the following medications within 12 weeks before receiving the first dose of study drug: gold salts (including oral gold), sulfasalazine (doses of up to 3 g/day were allowed), azathioprine, antimalarials, or penicillamine. Methotrexate was also allowed but could not have been begun or been altered within eight weeks prior to receiving the first dose of study medication for the pivotal studies. In the pivotal studies, patients could also have been on oral corticosteroids but could not have changed the dose regimen within four weeks before receiving the first dose of study medication (doses of up to 10 mg prednisone or equivalent/day were allowed), or had received intramuscular, intra-articular, or soft-tissue injections of corticosteroids within four weeks before receiving the first dose of study medication.

In supporting Study 012 patients could not have begun taking oral corticosteroids or methotrexate within 12 weeks or changed the dosage regimen within 8 weeks prior to their first dose of study medication. Intramuscular, intra-articular, or soft tissue

injections of corticosteroids were also disallowed within 12 weeks of treatment with study medication.

5.2.1.2 Scales Used for Measurement of RA Efficacy

For all studies, the analysis of celecoxib's efficacy in the treatment of the signs and symptoms of RA incorporated a large number of primary and secondary efficacy endpoints, some of which were the same as those used to analyze its effect in OA.

The primary RA efficacy endpoints included the following:

- Number of Swollen Joints (16)
- Number of Tender/Painful Joints (16)
- Patient's Global Assessment of Arthritic Condition (16)
- Physician's Global Assessment of Arthritic Condition (16)
- ACR-20 Responder Index (22)

The secondary RA efficacy endpoints included the following:

- Patient's Assessment of Arthritis Pain - VAS (15)
- Incidence of Withdrawal Due to Lack of Arthritis Efficacy
- Time to Withdrawal Due to Lack of Arthritis Efficacy
- ACR-50 Responder Index
- Tender/Painful Joints Score
- Swollen Joints Score
- Duration of Morning Stiffness
- Health Assessment Questionnaire (HAQ) Functional Disability Index (23)
- C-Reactive Protein

In addition, the ACR-70 Responder Index was performed as an exploratory analysis and quality-of-life was assessed using the SF-36 Health Assessment Questionnaire.

Efficacy evaluations were performed at Baseline, Week 2, Week 6, and Week 12 (or Early Termination) in each of the pivotal studies.

The primary population for analysis was the ITT cohort which was defined as all randomized patients who took at least one dose of the study drug. The LOCF method was used for imputing missing values.

In order to examine the overall effect of the study drug on the patient's condition, a categorical analysis was performed on all patients who met the ACR-20 criteria as improved compared to Baseline.

The ACR-20 criteria classifies a patient as "improved" if the patient experienced at least a 20% improvement from Baseline in the:

- Number of Tender/Painful Joints and
- Number of Swollen Joints;

as well as at least a 20% improvement from Baseline in three or more of the following five assessments:

- Physician's Global Assessment of Arthritic Condition,
- Patient's Global Assessment of Arthritic Condition,
- Patient's Assessment of Arthritis Pain - VAS,
- HAQ Functional Disability Index, and
- C-Reactive Protein.

Sixty-eight joints (right and left) were examined for Joint Tenderness/Pain. Artificial joints were not assessed. In response to pressure or motion, each joint was graded using the scale from 0 (none) to 3 (withdrawal by patient on examination).

Sixty-six joints were also graded for swelling using the scale from 0 (none) to 3 (bulging synovial proliferation with cystic characteristics). These joints were the same as those examined for tenderness except that the hip joints were not assessed.

Mean change analyses were performed for treatment comparisons for the above variables (with the exception of ACR-20 Responder Index) based on analysis of covariance models with center and treatment as factors and Baseline as a covariate. For ACR-20 Responder Index and other categorized variables, a categorical analysis based on the Cochran-Mantel-Haenszel test stratified by center was performed for treatment comparisons.

5.2.1.3 Patient Disposition

A total of 2250 patients with RA were entered into one of the two pivotal studies and randomized to receive one of five treatments for 12 weeks: celecoxib 100 mg BID, celecoxib 200 mg BID, celecoxib 400 mg BID, naproxen 500 mg BID, or placebo and were included in the ITT cohort. Table 15 presents a summary of all patients, by treatment group, who completed one of the 12-week pivotal studies. The reasons for study termination, grouped by treatment, for all randomized patients are also summarized this table.

Table 15. Reasons for Study Termination: 12-Week Pivotal RA Studies 022 and 023

	Number of Rheumatoid Arthritis Patients by Treatment Group				
		Celecoxib			Naproxen
Study	Placebo	100 mg BID	200 mg BID	400 mg BID	500 mg BID
Study 022	**(N=231)**	**(N=240)**	**(N=235)**	**(N=218)(a)**	**(N=225)**
Total Completed	**101 (44%)**	**154 (64%)**	**158 (67%)**	**137 (63%)**	**138 (61%)**
Total Withdrawn	**130 (56%)**	**86 (36%)**	**77 (33%)**	**81 (37%)**	**87 (39%)**
Treatment Failure	104 (45%)	67 (28%)	50 (21%)	59 (27%)	65 (29%)
Adverse Event	11 (5%)	13 (5%)	17 (7%)	12 (6%)	12 (5%)
Other	15 (5%)	6 (3%)	10 (4%)	10 (4%)	10 (4%)
Study 023	**(N=221)**	**(N=228)**	**(N=219)(a)**	**(N=217)**	**(N=218)**
Total Completed	**78 (35%)**	**117 (51%)**	**124 (57%)**	**126 (58%)**	**133 (61%)**
Total Withdrawn	**143 (65%)**	**111 (49%)**	**95 (43%)**	**91 (42%)**	**85 (39%)**
Treatment Failure	125 (57%)	92 (40%)	74 (34%)	69 (32%)	69 (32%)
Adverse Event	12 (5%)	12 (5%)	16 (7%)	16 (7%)	16 (7%)
Other	6 (3%)	7 (3%)	5 (2%)	6 (3%)	0 (0%)

a) Total number of patients includes two patients (one in the celecoxib 200 mg BID group [Study 023] and one in the celecoxib 400 mg BID group [Study 022]) who were randomized but did not receive study medication and are not included in the ITT cohort.

5.2.1.4 Patient Characteristics

Table 16 summarizes the pooled Baseline demographic characteristics and arthritis history for all patients enrolled in the two pivotal studies. In these studies, age, race, gender, arthritis history, and corticosteroid and DMARD use were comparable across treatment groups. The demographic characteristics, arthritis history and co-therapy for each individual study were consistent with the pooled results. Patients in the pivotal studies had long-standing arthritic disease as evidenced by an average RA duration in the pivotal trials of 10 years. In addition, approximately 75% of these patients were receiving DMARD co-therapy, and 40% were taking oral corticosteroids.

Table 16. Pooled Baseline Demographic Characteristics and Disease Status for RA Patients By Treatment Group: Pooled Pivotal RA Studies 022 and 023

Baseline Demographic Characteristic	Number of Patients by Treatment Group				
		Celecoxib			Naproxen
	Placebo (N=452)	100 mg BID (N=468)	200 mg BID (N=454)(a)	400 mg BID (N=435)(a)	500 mg BID (N=443)
Age (years)					
Mean (Std. Dev.)	54.2 (12.42)	55.1 (11.99)	54.0 (12.09)	54.0 (12.10)	55.9 (12.09)
Range	(b)(4)				
≥65 years - N (%)	102 (23%)	104 (22%)	103 (23%)	91 (21%)	122 (28%)
Race/Ethnic Origin					
Caucasian/Hispanic - N (%)	414 (92%)	419 (89%)	412 (91%)	392 (90%)	405 (91%)
Black - N (%)	36 (8%)	42 (9%)	35 (8%)	35 (8%)	34 (8%)
Other - N (%)	2 (<1%)	7 (1%)	7 (2%)	8 (2%)	4 (1%)
Gender					
Female - N (%)	336 (74%)	346 (74%)	328 (72%)	314 (72%)	313 (71%)
Disease Duration - Years					
Mean (Std. Dev.)	10.3 (9.91)	10.7 (±9.01)	10.4 (9.32)	10.3 (8.77)	11.0 (9.80)
Range	(b)(4)				
≥5 years - N (%)	293 (65%)	333 (71%)	288 (63%)	285 (66%)	300 (68%)
Corticosteroid Use					
Yes - N (%)	175 (39%)	209 (45%)	172 (38%)	154 (35%)	167 (38%)
Methotrexate Use					
Yes - N (%)	192 (42%)	221 (47%)	205 (45%)	202 (46%)	200 (45%)
Other DMARD Use					
Yes - N (%)	148 (33%)	153 (33%)	139 (31%)	132 (30%)	149 (34%)

a) Total number of patients includes two patients (one in the celecoxib 200 mg BID group [Study 023] and one in the celecoxib 400 mg BID group [Study 022]) who were randomized into a study but did not receive study medication and were not included in the ITT cohort.

5.2.1.5 Efficacy and Dose Response

In two 12-Week pivotal studies, the Number of Swollen Joints in RA patients treated with celecoxib doses of 100 mg BID, 200 mg BID, and 400 mg BID were statistically significantly reduced when compared to placebo at the Week 2 assessment and this improvement was maintained through the Week 6 and Week 12 assessments (Figure 14, Table 17). Similarly, for the other primary measures of efficacy, all celecoxib doses showed statistically significantly greater improvement when compared to placebo treatment at Week 12 (Figure 15, Tables 18 and 19) as well as all earlier assessments in both studies with few exceptions. A significant treatment effect was not detected in the Physician's Global Assessment or the HAQ Functional Disability Index at Week 12 in Study 022 for the celecoxib 100 mg BID treatment group and in Study 023, the treatment effect observed with ACR-20 Responders Index at Week 12 for the celecoxib 100 mg BID dose did not separate statistically from placebo.

Celecoxib doses of 100 mg BID and 200 mg BID were efficacious and escalating the dose to 400 mg BID did not offer improved efficacy in either of the 12-Week pivotal RA studies. The responses to celecoxib 200 mg BID and 400 mg BID were not statistically significantly different in either study at any assessment time for any primary measure of efficacy. Only one statistically significant difference was detected between celecoxib doses of 200 mg BID and 400 mg BID. This difference was in favor of celecoxib 200 mg BID and occurred in Study 022 for ACR-20 Responders Index at Week 6. The responses to celecoxib 100 mg BID and 400 mg BID for all primary measures of efficacy at Weeks 2, 6, and 12 were also not significantly different.

The responses of celecoxib 100 mg BID were generally similar to 200 mg BID across all primary measures of efficacy in Study 023 with the exception of significantly lower response in the ACR-20 Responders Index at Week 12. In Study 022, the responses to celecoxib 200 mg BID tended to be greater than celecoxib 100 mg BID, but were also greater than celecoxib 400 mg BID. These results indicate that some RA patients may derive additional benefit from the 200 mg BID dose of celecoxib when compared to celecoxib 100 mg BID.

In both of the pivotal studies, comparable efficacy of celecoxib 100 mg BID and 200 mg BID to naproxen 500 mg BID was demonstrated. Celecoxib 100 mg BID, 200 mg BID and 400 mg BID were not statistically significantly different from naproxen 500 mg BID for all primary measures of efficacy at nearly all assessment times in both pivotal studies. The comparison to naproxen further suggests that celecoxib 100 mg BID and 200 mg BID are efficacious and the most appropriate doses for treating the signs and symptoms of RA. As is the case with the placebo comparisons, increasing the dose of celecoxib to 400 mg BID provided no further benefit of improved efficacy in RA patients when compared to naproxen 500 mg BID.

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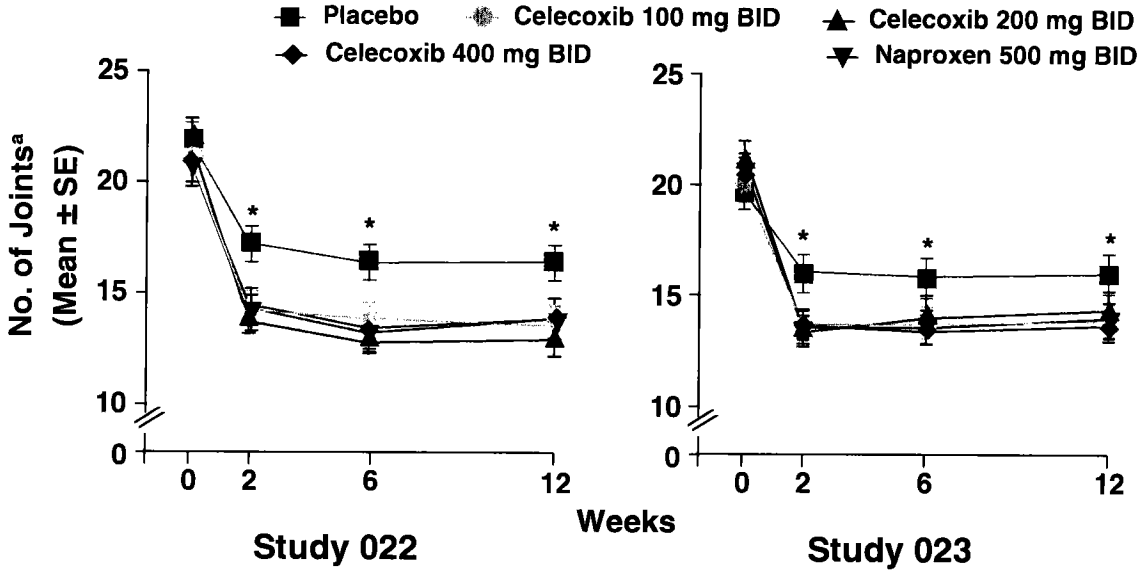
Figure 14. **Number of Swollen Joints: 12-Week Pivotal RA Studies 022 and 023**



* Significantly different from all active treatments; p<0.05.

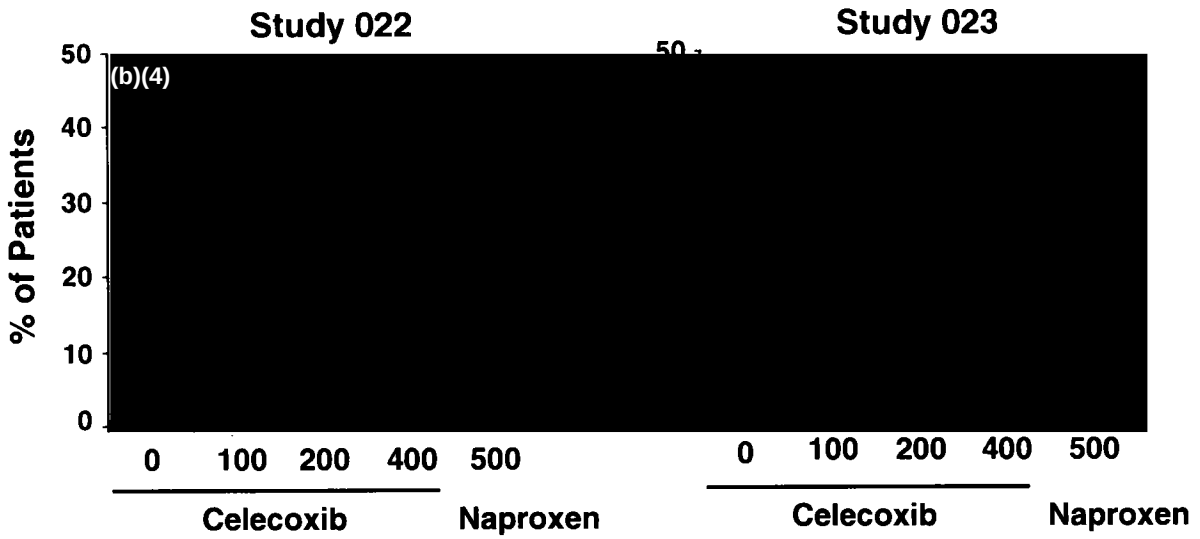
a) 66 joints examined

Table 17. **Changes from Baseline for Number of Swollen Joints and Number of Tender/Painful Joints: 12-Week Pivotal RA Studies 022 and 023**

	Study 022			Study 023		
Treatment Group	**N**	**Baseline**	**Change at Week 12**	**N**	**Baseline**	**Change at Week 12**
Swollen Joint Count (LS Mean Value)						
Placebo	231	22.2	-5.5	221	21.3	-3.7
Celecoxib 100 mg BID	240	21.0	-8.0*	228	21.4	-5.9*
Celecoxib 200 mg BID	235	22.1	-9.2*	218	22.6	-6.0*
Celecoxib 400 mg BID	217	20.8	-7.6*	217	22.3	-6.4*
Naproxen 500 mg BID	225	20.8	-7.6*	218	22.1	-6.1*
Tender/Painful Joint Count (LS Mean Value)						
Placebo	231	29.2	-8.2	221	30.1	-5.5
Celecoxib 100 mg BID	240	30.0	-12.0*	228	28.5	-10.0*
Celecoxib 200 mg BID	235	31.4	-12.3*	218	29.7	-10.2*
Celecoxib 400 mg BID	217	28.4	-12.4*	217	31.3	-11.1*
Naproxen 500 mg BID	225	28.9	-10.1	218	29.8	-11.2*

* Significantly different from placebo; p<0.05.

Figure 15. ACR-20 Responders Index - Percent of Patients Improved at Week 12: 12-Week Pivotal RA Studies 022 and 023



* Significantly different from placebo; p<0.05.
** Significantly different from celcoxib 100 mg BID; p<0.05.
Doses are mg BID

Table 18. HAQ Functional Disability Index: Baseline Mean Score and LS Mean Change from Baseline: 12-Week Pivotal RA Studies 022 and 023

Treatment Group	Study 022		Study 023	
	Baseline(a)	Change at Week 12	Baseline	Change at Week 12
Placebo	1.45	-0.10	1.42	-0.07
Celecoxib 100 mg BID	1.43	-0.17	1.44	-0.14*
Celecoxib 200 mg BID	1.52	-0.30*	1.38	-0.25*
Celecoxib 400 mg BID	1.44	-0.29*	1.35	-0.25*
Naproxen 500 mg BID	1.51	-0.22*	1.43	-0.22*

* Significantly different from placebo; p≤0.05).
a) Scale ranged from 0 to 3 with lower score as less disability.

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Table 19. Percent of Patients Improved from Baseline: 12-Week Pivotal RA Studies 022 and 023

Treatment Group	Study 022		Study 023	
	N	% Improved(a) at Week 12	N	% Improved(a) at Week 12
Patient's Global Assessment of Arthritic Condition (Categorical Change)				
Placebo	231	16	221	13
Celecoxib 100 mg BID	240	22*	228	18*
Celecoxib 200 mg BID	235	30*†‡	218	23*
Celecoxib 400 mg BID	217	25*	217	19*
Naproxen 500 mg BID	225	19	218	26*‡
Physician's Global Assessment of Arthritic Condition (Categorical Change)				
Placebo	231	15	221	12
Celecoxib 100 mg BID	240	21	228	18*
Celecoxib 200 mg BID	235	30*†‡	218	22*
Celecoxib 400 mg BID	217	25*	217	20*
Naproxen 500 mg BID	224	20	218	25*
ACR-20 Responder Index (Categorical Change)				
Placebo	231	29	221	23
Celecoxib 100 mg BID	240	40*	228	30
Celecoxib 200 mg BID	235	44*	218	39*‡
Celecoxib 400 mg BID	217	39*	217	36*
Naproxen 500 mg BID	225	36*	218	42*‡

* Significantly different from placebo; p<0.05.
† Significantly different from naproxen; p<0.05.
‡ Significantly different from celecoxib 100 mg BID; p<0.05.
a) Improvement is defined as reduction of at least 2 grades from Baseline for grades 3-5 or a change in grade from 2 to 1

5.2.1.6 Health-related Quality of Life: Rheumatoid Arthritis

The SF-36 Health Survey was administered at Baseline and at Weeks 2 and 12 of treatment in the 12-week pivotal RA studies (Studies 022 and 023). The mean scores at Baseline together with mean changes from Baseline to Week 12 for the eight domains of the SF-36 Health Survey for each study are shown in Table 20. Statistically significant improvements in Physical Functioning, Role-Physical, Bodily Pain, Vitality and Mental Health were observed in both studies for celecoxib 200 mg BID and celecoxib 400 mg BID. Similarly, significant treatment-related effects in these same domains were observed with celecoxib 100 mg BID and naproxen 500 mg BID in one or both studies. General Health and Role Emotional were found to significantly improve in all active treatment groups when compared to placebo in Study 022. In contrast, none of the active treatments was associated with significant improvement in Study 023 for these two domains.

Table 20. Baseline Mean Scores and Mean Changes from Baseline for SF-36 Quality-of-Life Domains: 12-Week Pivotal RA Trials 022 and 023

	Study 022		Study 023	
SF-36 Domain(a) Treatment Group	**Baseline**	**Change at Week 12**	**Baseline**	**Change at Week 12**
Physical Functioning				
Placebo	38.1	0.8	37.8	0.5
Celecoxib 100 mg BID	39.2	3.4	40.0	4.1*
Celecoxib 200 mg BID	36.4	9.5*	38.6	9.3*
Celecoxib 400 mg BID	38.6	8.7*	38.5	7.7*
Naproxen 500 mg BID	36.9	5.6*	37.1	7.0*
Role Physical				
Placebo	18.9	6.8	23.5	0.2
Celecoxib 100 mg BID	21.8	11.7	23.6	10.6*
Celecoxib 200 mg BID	23.1	15.7*	25.1	13.5*
Celecoxib 400 mg BID	22.7	14.0*	19.4	17.4*
Naproxen 500 mg BID	23.4	9.7	21.7	17.2*
Bodily Pain				
Placebo	32.9	2.3	35.0	-1.0
Celecoxib 100 mg BID	34.9	6.6*	34.6	7.1*
Celecoxib 200 mg BID	32.4	12.1*	34.1	11.5*
Celecoxib 400 mg BID	33.9	9.2*	32.5	11.6*
Naproxen 500 mg BID	34.4	8.2*	34.3	10.7*
General Health				
Placebo	51.5	-1.1	53.5	0.4
Celecoxib 100 mg BID	52.6	1.9*	52.3	2.6
Celecoxib 200 mg BID	50.6	3.6*	52.9	2.5
Celecoxib 400 mg BID	52.0	4.3*	52.2	2.4
Naproxen 500 mg BID	52.5	2.4*	50.0	5.4*
Vitality				
Placebo	34.7	-0.4	34.0	0.5
Celecoxib 100 mg BID	34.4	5.1*	36.6	6.9*
Celecoxib 200 mg BID	34.7	9.1*	35.7	6.9*
Celecoxib 400 mg BID	34.0	8.4*	33.5	9.9*
Naproxen 500 mg BID	35.2	4.8*	35.3	8.5*
Social Functioning				
Placebo	57.3	-2.7	61.3	-5.4
Celecoxib 100 mg BID	62.0	2.8*	62.2	3.5*
Celecoxib 200 mg BID	55.4	10.8*	61.6	7.4*
Celecoxib 400 mg BID	60.0	6.4*	60.3	7.8*
Naproxen 500 mg BID	60.2	3.1*	62.1	6.4*
Role Emotional				
Placebo	48.1	1.5	51.8	2.5
Celecoxib 100 mg BID	51.3	6.9*	57.9	-1.2
Celecoxib 200 mg BID	44.2	13.3*	57.7	3.9
Celecoxib 400 mg BID	52.9	5.2*	56.7	3.6
Naproxen 500 mg BID	46.4	9.8*	53.0	9.5
Mental Health				
Placebo	69.5	-1.4	69.4	-3.0
Celecoxib 100 mg BID	69.4	1.2	68.9	2.8*
Celecoxib 200 mg BID	65.6	4.3*	70.5	0.6
Celecoxib 400 mg BID	69.1	2.0*	69.3	2.9*
Naproxen 500 mg BID	66.7	3.7*	67.5	4.3*

* Significantly different from placebo; $p \leq 0.05$.

a) Scale ranged from 0 to 100 with lower score as worse for all domains.

5.2.2 Supportive RA Efficacy Studies

5.2.2.1 Placebo-Controlled Study: Study 012

Study 012 was a dose-ranging, double-blind, placebo-controlled, parallel-group, 4-week study to evaluate the efficacy of celecoxib 40 mg, 200 mg and 400 mg BID in treating the signs and symptoms of RA. Patients were eligible if they had RA that was in a flare state and had not received any NSAIDs in the two days prior to the first dose of study medication. Of the 330 ITT patients, 265 (80.3%) completed all 4 weeks of the study. For all primary efficacy variables, celecoxib produced a reduction in the signs and symptoms of RA. This improvement was statistically significant for the 200 mg and 400 mg dose groups at Week 1, Week 2, and Week 4; the only exception to this was the Number of Swollen Joints at Week 2 which was not statistically significant for either the 200 or 400 mg dose groups. The 40 mg celecoxib dose group was statistically superior to placebo only at Week 1 and only for the Patient's Global Assessment of Arthritic Condition and the Patient's Assessment of Pain (VAS).

5.2.2.2 International Active-Controlled RA Study: Study 041

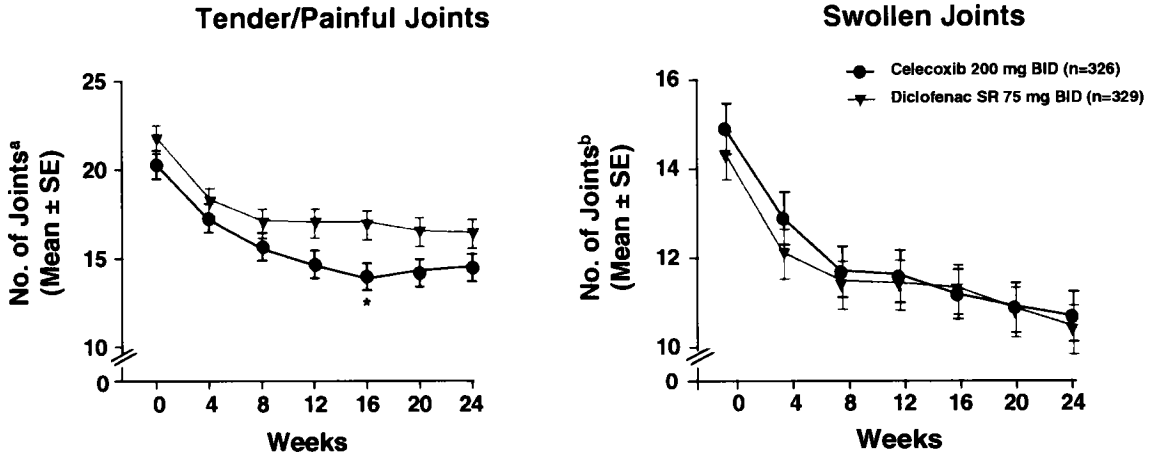
Study 041 was a randomized, double-blind, multicenter, parallel group trial designed to evaluate the efficacy and tolerability of celecoxib 200 mg BID as compared to diclofenac SR 75 mg BID in treating the signs and symptoms of RA.

To be enrolled, patients had to have met the ACR criteria for adult-onset RA that was clinically evident for at least six months prior to study enrollment. DMARD and oral corticosteroid co-therapy was allowed if it was stable for the 12 weeks prior to receiving the first dose of study medication. In addition, patients must have been anticipated to require continuous treatment with an anti-inflammatory drug to control arthritis symptoms for the duration of the study.

As illustrated in Tables 21 and 22, celecoxib provided clinically significant relief from the signs and symptoms of RA as measured by categorical change from Baseline in Patients and Physician's Global Assessments of Arthritic Condition. Similar results were observed for the Number of Tender/Painful Joints and the Number of Swollen Joints (Figure 16). For all primary efficacy analyses at all timepoints assessed, celecoxib and diclofenac SR 75 mg BID were similar. Among the primary measures of efficacy, there

was a statistically significant difference between the two treatments for only one assessment at one timepoint (Tender/Painful Joint Count at Week 16).

Figure 16. Numbers of Tender/Painful and Swollen Joints: Study 041



* Significantly different from diclofenac; $p<0.05$
a) 68 joints examined
b) 66 joints examined

Table 21. Tender/Painful and Swollen Joint Counts: Study 041

Treatment Group	N	Baseline	Change at Week 24*
Tender/Painful Joint Count (LS Mean Value)			
Celecoxib 200 mg BID	326	20.4	-5.8
Diclofenac SR 75 mg BID	329	21.7	-4.9
Swollen Joint Count (LS Mean Value)			
Celecoxib 200 mg BID	326	15.2	-3.9
Diclofenac SR 75 mg BID	329	14.6	-3.9

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Table 22. Summary of Categorical Primary Efficacy Analyses: Study 041

Treatment Group	N	% Improved at Week 24*
Patient's Global Assessment Categorical Change(a)		
Celecoxib 200 mg BID	326	40
Diclofenac SR 75 mg BID	329	40
Physician's Global Assessment Categorical Change(a)		
Celecoxib 200 mg BID	326	43
Diclofenac SR 75 mg BID	329	43
ACR-20 Responder Index Categorical Change(b)		
Celecoxib 200 mg BID	326	25
Diclofenac SR 75 mg BID	329	22

a) Improved: reduction of at least 1 grade from baseline.

b) Improved: at least 20% improvement from baseline in the number of tender/painful joints and in the number of swollen joints as well as at least 20% improvement from Baseline in at least 3 of the following assessments: Physician's Global, Patient's Global, Patient's Assessment of Arthritis Pain, C-Reactive Protein, and HAQ Functional Disability Index. HAQ Functional Disability Index was only available at Baseline and Week 24.

* There were no statistically significant differences between celecoxib and diclofenac.

5.2.2.3 Active-Controlled Studies: Studies 062 and 071

Study 062 was a randomized, double-blind, parallel group, multicenter, 12-week study designed primarily to compare the cumulative incidence of gastroduodenal ulcers associated with celecoxib 200 mg BID to that of naproxen 500 mg BID in patients with OA or RA. The efficacy of celecoxib compared to naproxen in RA patients was assessed in this trial but there were many fewer RA patients than OA patients. Patients were eligible to participate in the study if they had a documented clinical diagnosis of OA or RA (not necessarily in flare) and required chronic NSAID treatment. Overall, 359 (67.0%) of 536 ITT patients completed all 12 weeks of the study. There were no clinically significant differences between the celecoxib 200 mg BID and naproxen 500 mg BID treatment groups in the number of RA patients who showed improvement, no change, or worsening in arthritis condition at Weeks 4, 8, or 12.

Study 071 was a randomized, double-blind, parallel group, multicenter, 12-week study was designed primarily to compare the cumulative incidence of gastroduodenal ulcers associated with celecoxib 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA. However, efficacy and overall safety were also assessed during the trial. The efficacy of celecoxib compared to ibuprofen and diclofenac in RA patients was assessed in this trial, but there were many fewer RA patients than OA patients. Patients were eligible to participate in the study if they had a documented clinical diagnosis of OA or RA (not necessarily in flare) and required chronic NSAID treatment. Of the 1097 patients in the ITT cohort, 806 (73%) completed

12 weeks of study participation. There were no clinically significant differences between the celecoxib 200 mg BID, diclofenac 75 mg BID, and ibuprofen 800 mg TID treatment groups in the number of RA patients who showed improvement, no change, or worsening in arthritis condition at Weeks 4, 8, or 12.

5.2.3 Conclusions

Based on the results of replicate pivotal studies in RA patients, it is concluded that:

- Celecoxib doses of 100 mg BID, 200 mg BID, and 400 mg BID were efficacious in treating the signs and symptoms of RA.
- Although 100 mg BID and 200 mg BID provided similar efficacy overall, some patients may derive additional benefit from the 200 mg BID dose.
- No additional efficacy was obtained by increasing the dose of celecoxib above 400 mg per day.
- Celecoxib, at efficacious doses, had similar efficacy to full therapeutic doses of NSAIDs.
- Health-related quality of life improvements were observed with full therapeutic doses of celecoxib.

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5.3 Pain Management

Analgesic efficacy was assessed in a variety of clinical settings which included postsurgical pain models (oral surgery, orthopedic surgery, and general surgery) and pain associated with arthritis (OA and RA). Seven randomized and placebo-controlled studies were conducted in patients with postsurgical pain; six of these studies were double-blind and designed to be pivotal studies (025, 027, 070, 028, 029, and 080) (Table 23).

Table 23. Summary of Celecoxib Pain Management Studies

Study Number - Population	Duration	No. of Patients	Treatments
Post-Oral Surgery Studies			
025 - extraction of third molar(s)	single dose	250	Celecoxib 25, 50, or 200 mg; ibuprofen 400 mg; or placebo
027 - extraction of third molar(s)	single dose	220	Celecoxib 100 or 200 mg, naproxen sodium 550 mg, or placebo
070 - extraction of third molar(s)	single dose	255	Celecoxib 50, 100, 200, or 400 mg; naproxen sodium 550 mg; or placebo
005 - extraction of third molar(s)	single dose	200	Celecoxib 100 or 400 mg, aspirin 650 mg, or placebo
Post-Orthopedic and Post-General Surgery Studies			
028 - orthopedic surgery	up to 5 days	255	Celecoxib 100 or 200 mg (PRN up to BID) or Darvocet N® 100 mg (PRN up to QID)
029 - general surgery	up to 5 days	167	Celecoxib 100 or 200 mg (PRN up to BID) or Darvocet N® 100 mg (PRN up to QID)
080 - orthopedic surgery	up to 5 days	1	Celecoxib 200 mg (PRN up to BID) or naproxen 500 mg (PRN up to BID)

5.3.1 Post-Oral Surgery Studies

5.3.1.1 Pivotal Studies: Studies 025, 027 and 070

5.3.1.1.1 Population and Design

Studies 025, 027 and 070 were double-blind, randomized, placebo-controlled, single-dose post-oral surgery studies that contained an active control. In order to be entered into these studies, patients must have undergone surgical extraction of one (Study 070) or two (Studies 025 and 027) or more impacted third molar(s) requiring bone removal, one of which must have been mandibular, experiencing moderate to severe postsurgical pain, and rated their Baseline pain intensity ≥50 mm on a Visual Analog Scale (VAS) of 100 mm.

The Treatment Period was the 24-hour period immediately following the administration of a single dose of study medication. Patients underwent the scheduled pain assessments

at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 hours postdose. Patients were allowed to take rescue medication at any time in the study, however, they were then dropped from the study.

In total across the three post-oral surgery studies (Studies 025, 027, 070), patients were randomized to receive one of eight treatments: celecoxib 25 mg SD, celecoxib 50 mg SD, celecoxib 100 mg SD, celecoxib 200 mg SD, celecoxib 400 mg SD, naproxen sodium 550 mg SD, ibuprofen 400 mg SD, or placebo.

5.3.1.1.2 Description of the Efficacy Scales Used

The primary measures of efficacy for the postsurgical pain studies were (24):

- Time-Specific Pain Intensity Difference (PID) (Categorical). Pain intensity assessed by patients on a 4 point scale from 0 (none) to 3 (severe);
- Time-Specific Pain Relief (PR), assessed by patients on a 5 point scale from 0 (none) to 4 (complete);
- Time-Specific Sum of PID on a categorical scale and PR (PRID) at the postdose timepoints, best possible score is 7 (complete pain relief [PR=4] and change from severe pain at Baseline to no pain [PID=3]. Worst possible score is -1 (no pain relief [PR=0] and change from moderate pain at Baseline to severe pain [PID=-1]) ;
- Time to Rescue Medication, the difference between the start time for the rescue medication and the time the first dose of study drug was taken; and
- Time to Onset of Perceptible Pain Relief, assessed by instructing the patient to stop a stopwatch at the time of perceptible pain relief.

The secondary measures of efficacy were:

- Time-Specific Pain Intensity Difference (PID) (VAS);
- Sum of PID scores (SPID);
- Total Pain Relief (TOTPAR), the sum of the PR scores;
- Sum of PRID Scores (SPRID);
- Time to First Experienced 50% Pain Relief;
- Proportion of Patients Experiencing at Least 50% Pain Relief; and
- Proportion of Patients Experiencing 100% Pain Relief.

The remaining measures of efficacy, considered supportive, were:

- Peak Pain Intensity Difference (PPID);
- Peak Pain Relief (PPR);
- Patient Global Evaluation of Study Medication;
- APS Pain Measure; and
- Time to Onset of Meaningful Pain Relief.

The primary population for analysis was the ITT cohort, defined as all randomized patients who took one dose of study drug and did not take rescue medication prior to the one-hour timepoint. In addition, patients were excluded from the cohort if that patient had two consecutive scheduled timepoints in the first two hours obtained by interpolation from the same two observed data points. The last observation carried forward was used for imputing missing values. The analyses of the post-oral surgery studies focus on the first eight hours after administration of the single dose of study medication. A secondary consideration was the period of 8-24 hours after the single dose.

5.3.1.1.3 Patient Disposition

A total of 725 patients with post-oral surgery pain were enrolled into clinical studies with celecoxib and were included in the ITT cohort. Table 24 presents a summary of all patients, by treatment group, who completed each study. The reasons for study termination, grouped by treatment, for all randomized patients are also summarized in this table.

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Table 24. Reasons for Study Termination for Post-Oral Surgery Pain Patients: Studies 025, 027, 070

	Number of Postsurgical Patients by Treatment Group							
		Celecoxib					Naproxen Sodium	Ibuprofen
Study	Placebo	25 mg SD	50 mg SD	100 mg SD	200 mg SD	400 mg SD	550 mg SD	400 mg SD
Study 025								
Total Completed (a)	4 (8%)	4 (8%)	7 (14%)	---	13 (26%)	---	---	8 (16%)
Total Withdrawn	46 (92%)	46 (92%)	43 (86%)	---	37 (74%)	---	---	42 (84%)
Treatment Failure/ Rescue Medication	46 (92%)	46 (92%)	43 (86%)	---	37 (74%)	---	---	42 (84%)
Adverse Event	0 (0%)	0 (0%)	0 (0%)	---	0 (0%)	---	---	0 (0%)
Study 027								
Total Completed (a)	9 (16%)	---	---	17 (31%)	27 (48%)	---	28 (52%)	---
Total Withdrawn	46 (84%)	---	---	38 (69%)	29 (52%)	---	26 (48%) (b)	---
Treatment Failure/ Rescue Medication	46 (84%)	---	---	38 (69%)	29 (52%)	---	25 (46%)	---
Adverse Event	0 (0%)	---	---	0 (0%)	0 (0%)	---	0 (0%)	---
Study 070								
Total Completed (a)	2 (4%)	---	3 (9%)	10 (20%)	12 (24%)	13 (37%)	9 (26%)	---
Total Withdrawn	48 (96%)	---	32 (91%)	40 (80%)	38 (76%)	22 (63%)	26 (74%)	---
Treatment Failure/ Rescue Medication	48 (96%)	---	31 (89%)	40 (80%)	38 (76%)	22 (63%)	26 (74%)	---
Adverse Event	0 (0%)	---	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	---

a) Completed patient was defined as having completed evaluations through 24 hours (Studies 025, 027 and 070) without taking rescue medication.
b) One patient was discharged before the 24 hour assessment.

5.3.1.1.4 Patient Characteristics

Table 25 shows a descriptive summary of the pooled Baseline demographic characteristics for all patients enrolled in the 24-hour post-oral surgery studies (Studies 025, 027, 070).

Table 25. Pooled Baseline Demographic Characteristics for Post-Oral Surgery Pain Patients: Studies 025, 027, and 070

	Number of Postsurgical Patients by Treatment Group							
		Celecoxib					Naproxen Sodium	Ibuprofen
Baseline Demographic Characteristic	Placebo (N=155)	25 mg SD (N=50)	50 mg SD (N=85)	100 mg SD (N=105)	200 mg SD (N=156)	400 mg SD (N=35)	550 mg SD (N=89)	400 mg SD (N=50)
Age (years)								
Mean (Std Dev)	23.1 (4.43)	23.3 (5.72)	24.0 (5.50)	23.6 (5.61)	23.6 (5.28)	24.2 (5.97)	23.4 (5.64)	24.3 (5.48)
Range	(b)(4)							
Race/Ethnic Origin								
Caucasian/ Hispanic N (%)	137(88%)	46 (92%)	72 (85%)	93 (89%)	140 (90%)	31(89%	82 (92%)	47 (94%)
Black N (%)	12 (8%)	3 (6%)	9 (11%)	9 (9%)	10 (6%)	3 (9%)	4 (4%)	1 (2%)
Other N (%)	6 (4%)	1 (2%)	4 (5%)	3 (3%)	6 (3%)	1 (3%)	3 (3%)	2 (4%)
Gender								
Female N (%)	89 (57%)	32 (64%)	53 (62%)	60 (57%)	93 (60%)	21 (60%)	51 (57%)	40 (80%)

Within these studies, there were no clinically significant differences between any of the treatment groups with regard to age, race or gender with the exception of a higher proportion of females in the ibuprofen group (Study 025).

5.3.1.1.5 Efficacy and Dose Response

In replicate post-oral surgery studies, celecoxib doses of 100 mg (Studies 027 and 070) and 200 mg (Studies 025, 027, and 070) provided statistically significant Pain Relief (PR) compared to placebo beginning by one hour after dosing and continuing through eight hours (Figure 17, Table 26). Analogous results were observed in the PID and PRID (Table 26). Celecoxib doses below 100 mg were submaximally efficacious. A 400 mg dose of celecoxib was tested in Study 070. This dose did not provide statistically significantly greater analgesic efficacy when compared to the 100 mg and 200 mg doses of celecoxib over the entire eight hour post-dosing interval for the PID and PRID and for the first seven hours for the PR.

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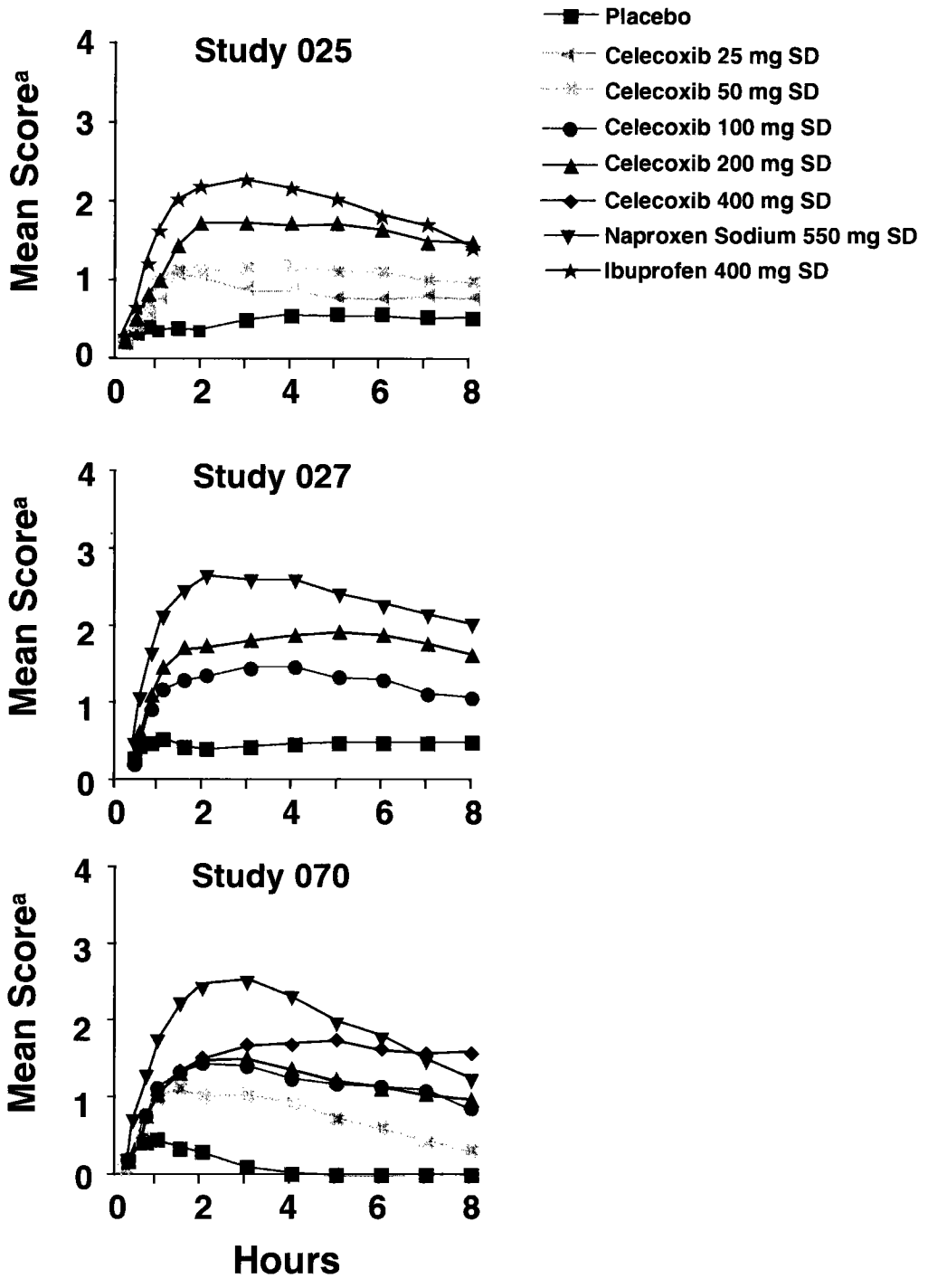
Figure 17. **Pain Relief: Pivotal Post-Oral Surgery Pain Studies 025, 027 and 070**



a) Scale ranges from 0 (none) to 4 (complete).

Table 26. Categorical Primary Efficacy Variables: Studies 025, 027 and 070

	Treatment Group	N	Time Postdose (Hours)				
			.75	1	2	6	8
Study 025	**Pain Relief (PR) - Categorical Mean Score**						
	Placebo	50	0.42	0.38	0.38	0.58	0.52
	Celecoxib 25 mg	50	0.58	0.78*	1.08*	0.78	0.80
	Celecoxib 50 mg	50	0.72	0.98*	1.12*	1.12*	1.00
	Celecoxib 200 mg	50	0.84*	1.02*	1.74*	1.66*	1.50*
	Ibuprofen 400 mg	50	1.22*	1.64*	2.20*	1.82*	1.42*
	Pain Intensity Difference (PID) - Categorical Mean Score						
	Placebo	50	-0.08	-0.14	-0.14	-0.02	-0.06
	Celecoxib 25 mg	50	0.08	0.14*	0.26*	0.12	0.12
	Celecoxib 50 mg	50	0.24*	0.38*	0.42*	0.38*	0.34*
	Celecoxib 200 mg	50	0.12	0.22*	0.56*	0.58*	0.52*
	Ibuprofen 400 mg	50	0.52*	0.72*	1.02*	0.86*	0.66*
	Pain Intensity Difference and Pain Relief (PRID) - Categorical Mean Score						
	Placebo	50	0.34	0.24	0.24	0.56	0.46
	Celecoxib 25 mg	50	0.66	0.92*	1.34*	0.90	0.92
	Celecoxib 50 mg	50	0.96*	1.36*	1.54*	1.50*	1.34*
	Celecoxib 200 mg	50	0.96*	1.24*	2.30*	2.24*	2.02*
	Ibuprofen 400 mg	50	1.74*	2.36*	3.22*	2.68*	2.08*
Study 027	**Pain Relief (PR) - Categorical Mean Score**						
	Placebo	55	0.55	0.60	0.51	0.60	0.62
	Celecoxib 100 mg	55	0.98*	1.24*	1.45*	1.53	1.33*
	Celecoxib 200 mg	56	1.18*	1.54*	1.88*	2.05*	1.80*
	Naproxen Sodium 550 mg	54	1.70*	2.17*	2.72*	2.44*	2.24*
	Pain Intensity Difference (PID) - Categorical Mean Score						
	Placebo	55	-0.09	-0.15	-0.20	-0.15	-0.13
	Celecoxib 100 mg	55	0.29*	0.36*	0.53*	0.56*	0.40*
	Celecoxib 200 mg	56	0.39*	0.55*	0.77*	0.88*	0.77*
	Naproxen Sodium 550 mg	54	0.69*	0.87*	1.26*	1.04*	0.93*
	Pain Intensity Difference and Pain Relief (PRID) - Categorical Mean Score						
	Placebo	55	0.45	0.45	0.31	0.45	0.49
	Celecoxib 100 mg	55	1.27*	1.60*	1.98*	2.09*	1.73*
	Celecoxib 200 mg	56	1.57*	2.09*	2.64*	2.93*	2.57*
	Naproxen Sodium 550 mg	54	2.39*	3.04*	3.98*	3.48*	3.17*
Study 070	**Pain Relief (PR) - Categorical Mean Score**						
	Placebo	50	0.50	0.54	0.48	0.32	0.48
	Celecoxib 50 mg	35	0.86	1.06*	1.26*	0.91*	1.26*
	Celecoxib 100 mg	50	0.84	1.20*	1.58*	1.42*	1.58*
	Celecoxib 200 mg	50	0.84	1.14*	1.64*	1.36*	1.64*
	Celecoxib 400 mg	35	0.83	1.11*	1.66*	1.89*	1.66*
	Naproxen Sodium 550 mg	35	1.34*	1.80*	2.49*	1.89*	2.49*
	Pain Intensity Difference (PID) - Categorical Mean Score						
	Placebo	50	0.08	0.14	0.04	-0.08	-0.08
	Celecoxib 50 mg	35	0.20	0.31	0.49*	0.29*	0.20
	Celecoxib 100 mg	50	0.34	0.56*	0.78*	0.72*	0.56*
	Celecoxib 200 mg	50	0.40	0.60*	0.84*	0.74*	0.70*
	Celecoxib 400 mg	35	0.23	0.43	0.66*	0.77*	0.74*
	Naproxen Sodium 550 mg	35	0.51*	0.77*	1.26*	0.91*	0.60*
	Pain Intensity Difference and Pain Relief (PRID) - Categorical Mean Score						
	Placebo	50	0.58	0.68	0.52	0.24	0.24
	Celecoxib 50 mg	35	1.06	1.37	1.74*	1.20*	0.91
	Celecoxib 100 mg	50	1.18	1.76*	2.36*	2.14*	1.76*
	Celecoxib 200 mg	50	1.24	1.74*	2.48*	2.10*	1.98*
	Celecoxib 400 mg	35	1.06	1.54*	2.31*	2.66*	2.60*
	Naproxen Sodium 550 mg	35	1.86*	2.57*	3.74*	2.80*	2.03*

* Significantly different from placebo; $p<0.05$.

Celecoxib at doses of 100 and 200 mg was associated with a significantly longer duration of effect when compared to placebo in two or more of the post-oral surgery pain studies (Table 27). The median Time to Rescue Medication was longer with higher doses of celecoxib; however, no statistically significant differences were detected between the 100, 200, and 400 mg treatment groups or the distribution of time to rescue medication. The Median Times to Onset of Perceptible Pain Relief for Studies 025, 027, and 070 are also shown in Table 27. Statistically significant differences were observed for celecoxib 50 mg (Study 025), 100 mg (Study 027) and 200 mg (Studies 025 and 027).

Table 27. Temporal Primary Efficacy Variables: Studies 025, 027, and 070

	Study 025		Study 027		Study 070	
Efficacy Assessment	**N**	**Median Time**	**N**	**Median Time**	**N**	**Median Time**
Time to Rescue Medication						
Placebo	50	01:17	55	01:20	50	01:06
Celecoxib 25 mg	50	01:32	-	-	-	-
Celecoxib 50 mg	50	01:48*	-	-	35	01:41*
Celecoxib 100 mg	-	-	55	04:17*	50	02:36*
Celecoxib 200 mg	50	03:05*	56	10:02*	50	04:15*
Celecoxib 400 mg	-	-	-	-	35	08:13*
Ibuprofen 400 mg	50	07:00*	-	-	-	-
Naproxen Sodium 550 mg	-	-	54	>24:00*	35	07:00*
Time to Perceptible Pain Relief						
Placebo	50	>24:00	55	00:58	50	>24:00
Celecoxib 25 mg	50	00:53	-	-	-	-
Celecoxib 50 mg	50	01:05*	-	-	35	00:42
Celecoxib 100 mg	-	-	55	00:45	50	00:39
Celecoxib 200 mg	50	00:38*	56	00:30*	50	00:44
Celecoxib 400 mg	-	-	-	-	35	00:43
Ibuprofen 400 mg	50	00:33*	-	-	-	-
Naproxen Sodium 550 mg	-	-	54	00:24*	35	00:36

* Significantly different from placebo based on log rank test as in Fisher's Protected LSD; p<0.05.

5.3.1.2 Supportive Study: Study 005

Study 005 was a single-center, single-dose, randomized, placebo-controlled, single-blind, parallel group study designed to investigate the safety and analgesic efficacy of celecoxib in patients who had undergone surgical third molar extraction. Following dental surgery, patients experiencing moderate to severe pain received a single dose of celecoxib 100 mg, celecoxib 400 mg, aspirin 650 mg, or placebo.

A total of 50 patients per treatment group (200 total) were enrolled into the study all of whom received treatment and were included in the ITT cohort. For the three categorical primary measures of efficacy (PID, PR, and PRID) single oral doses of celecoxib at dose

levels of 100 and 400 mg provided statistically superior pain relief compared to placebo at all postdose assessment times after 0.5 hours. Similar responses were observed in aspirin-treated patients. Statistically significant differences were noted between aspirin and celecoxib at various timepoints, generally favoring aspirin up to 1 hour and favoring celecoxib between three and four hours after dosing. Median Time to Rescue was statistically significantly better for the celecoxib 100, and 400 mg treatment groups compared to placebo. Aspirin was also statistically superior to placebo for this temporal endpoint.

5.3.2 Post-Orthopedic Surgery Study: Study 028

5.3.2.1 Pivotal Study

5.3.2.1.1 Population and Design

Study 028 was a multicenter, multiple dose, double-blind, placebo-controlled, randomized, parallel group study designed to compare the analgesic efficacy of celecoxib 100 and 200 mg PRN up to BID to propoxyphene napsylate 100 mg with acetaminophen 650 mg (two Darvocet-N® 50) PRN up to QID, and placebo in post-orthopedic surgery patients with moderate to severe pain.

Patients were eligible to participate in the study if they had undergone orthopedic surgery involving a total or partial reconstruction procedure of the hip or knee or a major orthopedic procedure requiring open manipulation of bone with periosteal elevation.

The Treatment Period was defined as up to a five day period after the first dose of study medication. Patients received the second dose of study medication not less than four hours after the first dose of study medication. Subsequent doses of study medication were administered as needed, no closer than two hours apart, and could not exceed four doses in 24 hours. In the celecoxib groups, only the first two doses were active, doses three and four were matching placebo. In contrast, all four doses of Darvocet-N 50 (2 tablets) were active.

5.3.2.1.2 Description of Efficacy Scales Used

Primary measures of efficacy were (24):

- Time-Specific PID (Categorical)
- PR

- PRID
- Time to Rescue Medication or Remedication

Although the duration of treatment was up to five days and patients assessed pain at Baseline (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18 and 24 hours postdose (using self-rating scales), the primary analyses emphasized the first eight hours after the first dose was taken, in order to determine the efficacy response to a single dose. A secondary objective of this study was to compare the efficacy of celecoxib with placebo for the remainder of the first 24-hour period after dosing. The 24-hour analysis focused on multiple dose data.

5.3.2.1.3 Patient Disposition

A total of 246 patients were randomized and included in the ITT cohort. Three patients completed the 5-day study; the majority of patients were withdrawn for treatment failure.

5.3.2.1.4 Patient Characteristics

Baseline demographics for Study 028 are presented in Table 28. There were no meaningful differences across treatment groups in age, race, or gender.

Table 28. Baseline Demographic Characteristics for Post-Orthopedic Surgery Patients: Study 028

Baseline Demographic Characteristic	Number of Postsurgical Patients by Treatment Group(a)			
	Placebo (N=60)	Celecoxib 100 mg BID PRN (N=68)	Celecoxib 200 mg BID PRN (N=62)	Darvocet-N 100 mg QID PRN (N=65)
Age (years)				
Mean (Std Dev)	52.2 (16.52)	55.7 (16.35)	59.0 (16.10)	56.4 (15.73)
Range	(b)(4)			
Race/Ethnic Origin				
Caucasian/Hispanic N (%)	53 (88%)	63 (92%)	61 (98%)	57 (88%)
Black N (%)	7 (12%)	3 (4%)	1 (2%)	5 (8%)
Other N (%)	0 (0%)	2 (3%)	0 (0%)	3 (5%)
Gender				
Female N (%)	30 (50%)	31 (46%)	28 (45%)	29 (45%)

a) Table includes nine patients who were randomized but were excluded from the ITT cohort.

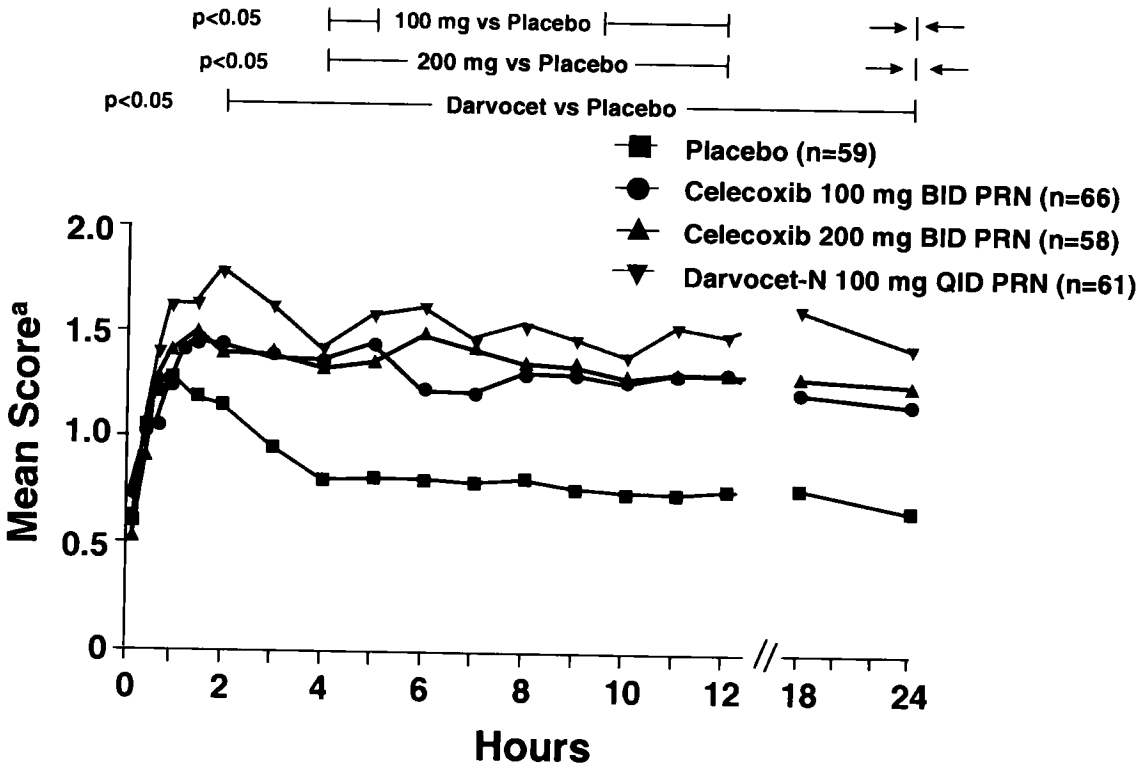
5.3.2.1.5 Efficacy and Dose Response

The results of the single-dose analyses demonstrate that, for all categorical primary measures of efficacy (PID, PR, PRID) over the first eight hours, celecoxib 100 mg and celecoxib 200 mg were numerically superior to placebo in providing relief from post-surgical pain at all timepoints after 0.5 hours (except 100 mg at 1 hour for PID) (data not

shown). There were isolated instances within some, but not all, measures in which celecoxib 100 or 200 mg was statistically significant when compared to placebo. The sensitivity to detect statistically significant differences in treatment effect from placebo was limited by the unexpectedly large placebo response at the early assessment times.

In the multiple dose analyses which continued up through the 24-hour timepoint, analgesic efficacy of multiple doses of celecoxib was indicated by the numerically greater mean PID (Categorical Scale), PR, and PRID scores for both the 100 and 200 mg BID PRN treatment groups, compared to placebo, at all timepoints from 0.75 hours to 24.0 hours (Figure 18 and Table 29). These differences were statistically significant at most assessment times from 4.0 hours through 24.0 hours for the celecoxib 200 mg BID PRN treatment group compared to placebo. Statistically significant differences favoring the celecoxib 100 mg BID PRN treatment group over placebo were also noted for mean PR after the 4.0 hour timepoint.

Figure 18. Pain Relief (Multiple Dose Analysis): Study 028



a) Scale ranges from 0 (none) to 4 (complete).

Table 29. Results of Categorical Primary Efficacy Analyses (Multiple Dose Analysis): Study 028

Efficacy Assessment	N	Time Postdose (Hours)						
		1	2	4	8	12	18	24
Pain Relief (PR) - Categorical Mean Score								
Placebo	59	1.25	1.10	0.77	0.78	0.73	0.74	0.64
Celecoxib 100 mg BID PRN	66	1.39	1.42	1.34*	1.26	1.28*	1.18	1.13*
Celecoxib 200 mg BID PRN	58	1.41	1.40	1.33*	1.36*	1.31*	1.30	1.26*
Darvocet-N 100 mg QID PRN	61	1.63	1.74*	1.40*	1.47*	1.44*	1.58*	1.34*
Pain Intensity Difference (PID) - Categorical Mean Score								
Placebo	59	0.50	0.44	0.19	0.19	0.15	0.17	0.12
Celecoxib 100 mg BID PRN	66	0.46	0.49	0.39	0.38	0.36	0.31	0.21
Celecoxib 200 mg BID PRN	58	0.66	0.63	0.50	0.57*	0.53*	0.57*	0.48*
Darvocet-N 100 mg QID PRN	60	0.80*	0.92*	0.69*	0.68*	0.65*	0.70*	0.55*
Pain Intensity Difference and Pain Relief (PRID) - Categorical Mean Score								
Placebo	59	1.75	1.54	0.96	0.97	0.88	0.91	0.76
Celecoxib 100 mg BID PRN	66	1.85	1.91	1.73	1.64	1.64	1.48	1.34
Celecoxib 200 mg BID PRN	58	2.07	2.03	1.83*	1.93*	1.85*	1.88*	1.74*
Darvocet-N 100 mg QID PRN	61	2.43	2.66*	2.09*	2.15*	2.09*	2.28*	1.89*

* Significantly different from placebo; $p<0.05$.

The Time to Rescue Medication or Remedication is displayed in Table 30. Median Time to Rescue Medication or Remedication after the first dose of study medication was longer in both celecoxib treatment groups compared to placebo but the difference was only statistically significant for the 100 mg BID group. Additional evidence of the analgesic efficacy of the celecoxib multiple dose regimen was provided by the proportion of patients who remained in the study 24 hours after the first dose. The proportion of patients remaining in the study at the 24-hour timepoint was similar for the three active treatment groups in contrast to the placebo group which had fewer patients than all active treatment groups at 24 hours (Table 30). These results indicate that celecoxib doses of 100 or 200 mg, administered as needed every 4-6 hours up to a maximum daily dose of 400 mg are efficacious in the management of pain.

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Table 30. Variables Indicating Effect of Dose Regimen: Study 028

Time to Rescue Medication or Remedication (a)		
	N	Median Time (Hours : Minutes)
Placebo	59	03:33
Celecoxib 100 mg BID PRN	67	04:01*
Celecoxib 200 mg BID PRN	58	03:52
Darvocet-N 100 mg QID PRN	62	04:05*
Proportion of Patients Remaining in this Study at 24 Hours After the First Dose (b)		
	N	Patients
Placebo	59	4/59 (7%)
Celecoxib 100 mg BID PRN	67	16/67 (24%)*
Celecoxib 200 mg BID PRN	58	11/58 (19%)
Darvocet-N 100 mg QID PRN	62	17/62 (27%)*

* Significantly different from placebo; $p<0.05$.
a) Statistical significance calculated by Log Rank Test.
b) Statistical significance calculated by Fisher's Exact Test.

5.3.3 Post-General Surgery Study: Study 029

Study 029 was a multicenter, multiple dose, double-blind, placebo-controlled, randomized, parallel group study designed to compare the analgesic effect of celecoxib 100 mg BID PRN and celecoxib 200 mg BID PRN to propoxyphene napsylate 100 mg with acetaminophen 650 mg (two Darvocet-N® 50) QID PRN, and placebo in post-general (non-orthopedic) surgery patients with moderate to severe pain.

An interim analysis was performed on this study by an independent Data Monitoring Committee to evaluate the validity of the pain model. The analysis did not show differences between Darvocet-N 100 mg QID PRN or celecoxib at either dose and placebo sufficient to validate the model. Therefore, the Committee recommended cessation of the trial.

5.3.4 Analgesia Data from OA and RA Studies

5.3.4.1 Study Populations and Designs

Data from the pivotal arthritis trials, five in OA (Studies 020, 021, 054, 060, and 087) and two in RA (022 and 023) were analyzed in order to further assess celecoxib's efficacy in the management of pain. This analysis of pain management incorporated the results of primary and secondary efficacy endpoints specifically indicative of pain relief.

5.3.4.2 Description of the Efficacy Scales Used

Pain-specific primary and secondary efficacy endpoints from the OA and RA trials were combined for analysis to assess celecoxib's efficacy in an additional pain model.

For this summary, one measure of arthritis pain was selected for each type of trial. However, the measure selected was representative of the consistent analgesic response seen with all other pain measures that were used. The display of efficacy in OA pain is based on the APS Pain Measure, (20) and efficacy in RA pain is demonstrated based on the Patient's Assessment of Arthritis Pain - VAS. (15)

The APS Pain Measure consisted of five questions that assess the intensity and duration of pain experienced by patients (Table 31). The first question required a yes or no response. The remaining questions required rating the pain and its interference with daily activities on a scale of 0 (no pain) to 10 (worst pain possible). Patients completed the APS Pain Measure at Baseline and daily, thereafter, for the first seven days of dosing with study medication.

Table 31. APS Pain Scale

	Question	Scale
1	Have you experienced any pain in the past 24 hours?	yes/no
2	How much pain are you having right now?	0-10
3	Indicate the worst pain you have had in the past 24 hours.	0-10
4	Indicate the average level of pain you have had in the past 24 hours.	0-10
5	Indicate how pain has interfered with you in:	
	• General Activity	0-10
	• Mood	0-10
	• Walking Ability	0-10
	• Relations with other People	0-10
	• Sleep	0-10
	• Normal Work, Including Housework	0-10
	• Enjoyment of Life	0-10

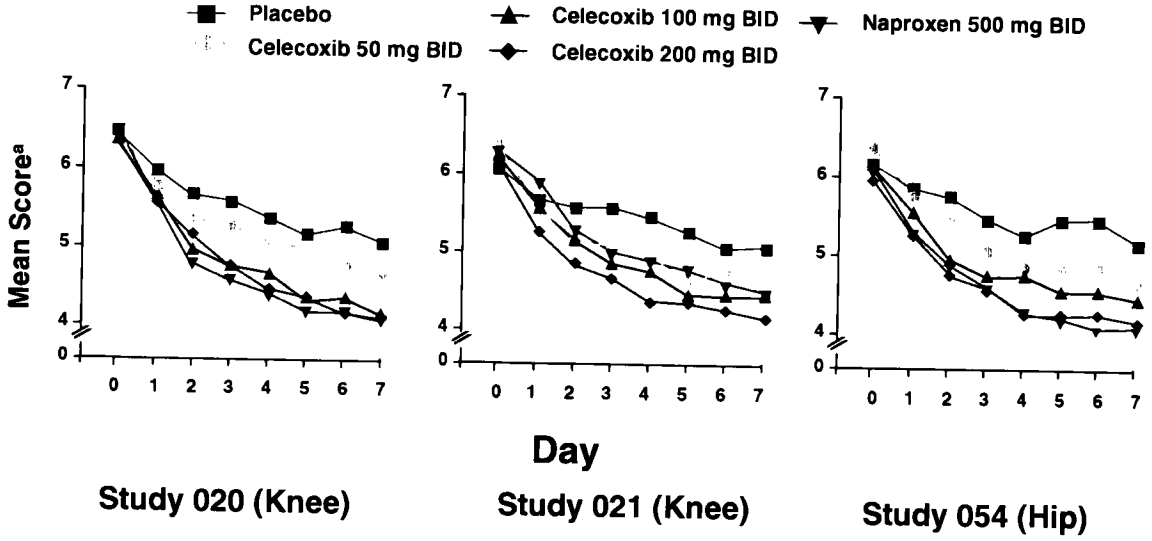
The Patient's Assessment of Arthritis Pain - VAS was performed for patient-identified "Index Joints." Patients assessed the amount of arthritis pain in the "Index Joint" on a 100 mm line VAS with the 0 mm point indicating no pain and 100 mm point indicating very severe pain.

5.3.4.3 Efficacy and Dose Response

5.3.4.3.1 Pain Analyses in Patients with OA: Studies 020, 021 and 054

The APS Pain Measure was used to assess acute analgesic activity of celecoxib in patients with OA flare in Studies 020, 021, and 054. The results of this analysis as represented by the results of the questions "Indicate the average level of pain you have had in the past 24 hours" and "Indicate the worst pain you have had in the past 24 hours" are presented graphically, in Figures 19 and 20 and Tables 32 and 33.

Figure 19. APS Pain Measure - Average Pain in Last 24 Hours: 12-Week Pivotal OA Studies 020, 021 and 054



a) Scale ranges from 0 (no pain) to 10 (worst pain possible)

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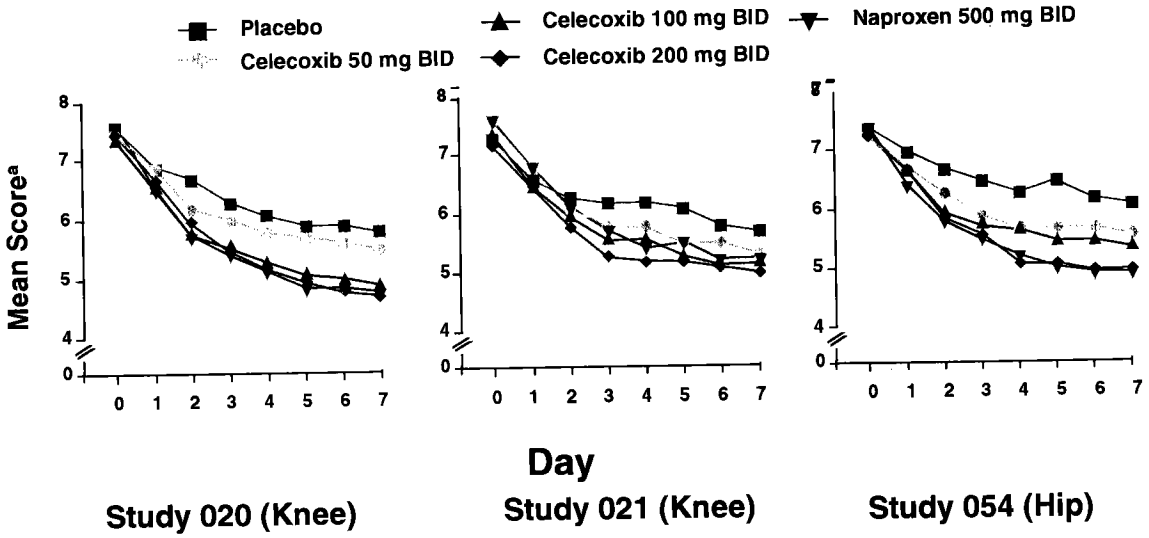
Figure 20. APS Pain Measure - Worst Pain in Last 24 Hours: 12-Week OA Studies 020, 021 and 054



a) Scale ranges from 0 (no pain) to 10 (worst pain possible)

The results of all five components of the APS Pain measure were similar. For four of the APS Pain Measure questions, celecoxib 100 and 200 mg BID were statistically significantly superior compared to placebo within 24 to 48 hours of the first dose of study medication and continuing through Day 7. For the question "Have you experienced any pain in the past 24 hours?", significantly more patients in the celecoxib 100 mg BID and 200 mg BID treatment groups answered "no" compared to the placebo group on some, but not all, of the days during the one-week assessment period in Studies 020 and 021 and only on Day 7 in Study 054.

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Table 32. APS Pain Measure - Average Pain in the Past 24 Hours: 12-Week Pivotal OA Studies 020, 021 and 054

Treatment Group	N	Baseline Mean(a)	Observed Mean by Observation Day						
			1	2	3	4	5	6	7
Study 020									
Placebo	145	6.4	5.9	5.6	5.5	5.3	5.1	5.2	5.0
Celecoxib 50 mg BID	142	6.4	5.7	5.3*	5.2	5.0	4.9	4.7	4.6
Celecoxib 100 mg BID	143	6.3	5.6	4.9*	4.7*	4.6*	4.3*	4.3*	4.1*
Celecoxib 200 mg BID	141	6.4	5.5	5.1*	4.7*	4.4*	4.3*	4.1*	4.0*
Naproxen 500 mg BID	144	6.4	5.5	4.7*	4.5*	4.3*	4.1*	4.1*	4.0*
Study 021									
Placebo	169	6.0	5.6	5.5	5.5	5.4	5.2	5.0	5.0
Celecoxib 50 mg BID	170	6.3	5.5*	5.1*	5.0*	4.9*	4.6*	4.7*	4.4*
Celecoxib 100 mg BID	165	6.2	5.5*	5.1	4.8*	4.7*	4.4*	4.4*	4.4*
Celecoxib 200 mg BID	159	6.1	5.2*	4.8*	4.6*	4.3*	4.3*	4.2*	4.1*
Naproxen 500 mg BID	169	6.2	5.8	5.2*	4.9*	4.8*	4.7*	4.5*	4.4*
Study 054									
Placebo	211	6.1	5.8	5.7	5.4	5.2	5.4	5.4	5.1
Celecoxib 50 mg BID	210	6.3	5.7	5.4*	5.0*	4.8*	4.8*	4.8*	4.6*
Celecoxib 100 mg BID	205	6.1	5.5*	4.9*	4.7*	4.7*	4.5*	4.5*	4.4*
Celecoxib 200 mg BID	202	5.9	5.2*	4.7*	4.5*	4.2*	4.2*	4.2*	4.1*
Naproxen 500 mg BID	202	6.0	5.2*	4.8*	4.5*	4.2*	4.1*	4.0*	4.0*

* Significantly different from placebo; p≤0.05.
a) Based on a scale of 0-10.

Table 33. APS Pain Measure - Worst Pain in the Past 24 Hours: 12-Week Pivotal OA Studies 020, 021 and 054

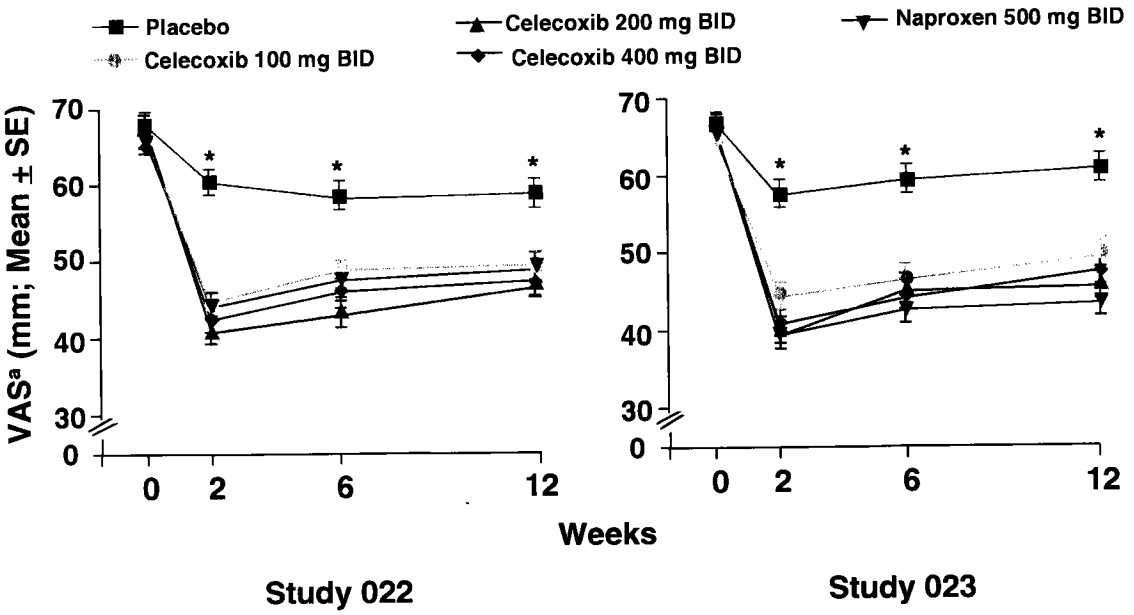
Treatment Group	N	Baseline Mean(a)	Observed Mean by Observation Day						
			1	2	3	4	5	6	7
Study 020									
Placebo	144	7.5	6.8	6.6	6.2	6.0	5.8	5.8	5.7
Celecoxib 50 mg BID	140	7.4	6.8	6.1	5.9	5.7	5.6	5.5	5.4
Celecoxib 100 mg BID	143	7.3	6.5	5.7*	5.5*	5.3*	5.0*	4.9*	4.8*
Celecoxib 200 mg BID	142	7.4	6.6	5.9*	5.4*	5.1*	5.0*	4.7*	4.6*
Naproxen 500 mg BID	144	7.5	6.4*	5.6*	5.3*	5.0*	4.7*	4.7*	4.6*
Study 021									
Placebo	170	7.2	6.5	6.2	6.1	6.1	6.0	5.7	5.6
Celecoxib 50 mg BID	172	7.5	6.7	6.0	5.7*	5.7*	5.4*	5.4*	5.2
Celecoxib 100 mg BID	165	7.3	6.4	5.9	5.5*	5.5*	5.2*	5.1*	5.1*
Celecoxib 200 mg BID	159	7.1	6.4	5.7	5.2*	5.1*	5.1*	5.0*	4.9*
Naproxen 500 mg BID	169	7.5	6.7	6.0	5.6*	5.3*	5.4*	5.1*	5.1*
Study 054									
Placebo	211	7.3	6.9	6.6	6.4	6.2	6.4	6.1	6.0
Celecoxib 50 mg BID	211	7.2	6.6	6.2*	5.8*	5.6*	5.6*	5.6*	5.5*
Celecoxib 100 mg BID	205	7.3	6.6*	5.9*	5.7*	5.6*	5.4*	5.4*	5.3*
Celecoxib 200 mg BID	206	7.2	6.6*	5.8*	5.5*	5.0*	5.0*	4.9*	4.9*
Naproxen 500 mg BID	202	7.3	6.3*	5.7*	5.4*	5.1*	4.9*	4.8*	4.8*

* Significantly different from placebo; p≤0.05.
a) Based on a scale of 0-10.

5.3.4.3.2 Pain Analyses in Patients with Rheumatoid Arthritis: Studies 022 and 023

Patient's Assessment of Pain (VAS) was used to assess the effects of celecoxib in patients with RA flare in Studies 022 and 023. As shown in Figure 21, all doses of celecoxib provided statistically significant reductions in pain compared to placebo by the Week 2 assessment and continuing through Week 12 in each of the 12-Week pivotal studies.

Figure 21. Patient's Assessment of Arthritis Pain - VAS: 12-Week Pivotal RA Studies 022 and 023



* Significantly different from all other treatments; p<0.05
a) Visual analog scale ranges from 0 (no pain) to 100 mm (most severe pain)

5.3.5 Conclusions

Based on the results of controlled trials in postsurgical pain, OA, and RA, it is concluded that:

- Evidence of the efficacy of celecoxib in alleviating pain was replicated in well-controlled clinical trials.
- For postsurgical pain:
  - Single doses of celecoxib of 100 mg, 200 mg, and 400 mg were efficacious.
  - Although 100 mg and 200 mg were similar in efficacy, some patients may derive additional benefit from the 200 mg dose.

- Celecoxib 100 mg or 200 mg administered as needed every 4-6 hours up to a maximum total daily dose of 400 mg was efficacious in the management of pain.

- Replicate well-controlled OA and RA trials confirmed the efficacy of celecoxib in the management of pain.

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6.0 CLINICAL SAFETY

6.1 Gastrointestinal Differentiation

6.1.1 Overview

As a specific inhibitor of COX-2, celecoxib was hypothesized to have anti-inflammatory and analgesic efficacy through COX-2 inhibition in the absence of deleterious GI effects resulting from COX-1 inhibition. To test this hypothesis, the effects of celecoxib on the GI tract were studied in prospective clinical trials. The focus was on two outcomes that are considered to be the most relevant in assessing GI mucosal toxicity: development of gastroduodenal ulcers, and occurrence of clinically significant upper gastrointestinal (UGI) events. The initiatives included 1) six clinical studies to determine the ulceration rate associated with celecoxib at therapeutic and supratherapeutic doses in comparison to NSAIDs and placebo (Table 34), and 2) a rigorous monitoring program to identify clinically significant UGI events in studies of arthritis patients receiving both therapeutic and supratherapeutic doses of celecoxib.

Table 34. Summary of Celecoxib GI Differentiation Studies

Study No. - Population	Duration	No. of Patients	Treatments
021 - Knee OA Flare	12 weeks	1215	Celecoxib 50, 100, or 200 mg BID; naproxen 500 mg BID; or placebo
022 - RA Flare	12 weeks	1149	Celecoxib 100, 200, or 400 mg BID; naproxen 500 mg BID; or placebo
041 - RA	24 weeks	655	Celecoxib 200 mg BID or diclofenac SR 75 mg BID
062 - OA or RA	12 weeks	537	Celecoxib 200 mg BID or naproxen 500 mg BID
071 -OA or RA	12 weeks	1099	Celecoxib 200 mg BID, diclofenac 75 mg BID, or ibuprofen 800 mg TID
014 - Healthy Subjects	7 days	128	Celecoxib 100 or 200 mg BID, naproxen 500 mg BID, or placebo

6.1.2 12-Week and 24-Week Endoscopy Studies

Five randomized, double-blind, endoscopy studies were performed with OA or RA patients receiving celecoxib or an NSAID. Two of the studies (Studies 021 and 022) also included a placebo group and served as pivotal efficacy trials.

In four studies, a Baseline endoscopy was performed (Studies 021, 022, 062, and 071). In these studies, patients with a gastric or duodenal ulcer were excluded from study participation. In the fifth study (Study 041) Baseline endoscopy was not performed and only patients enrolled at preselected sites underwent endoscopy during treatment.

Selection of the sites that performed endoscopy was determined by the feasibility of performing endoscopies.

For all endoscopies, the gastric and duodenal mucosae were examined and graded separately. In the ulcer analyses, a patient was counted as having a gastroduodenal ulcer if either a gastric or duodenal ulcer (or both) was present. The studies employed varying endoscopy schedules. In Studies 021 and 022, endoscopy was performed at Baseline and at the end of 12 weeks of treatment. Studies 062 and 071 employed a multiple endoscopy design in which endoscopy was performed at Baseline and after four, eight, and 12 weeks of treatment. In Study 041, endoscopy was performed after 24 weeks of treatment. In addition to the scheduled endoscopies, patients withdrawing from any of these studies before completion were asked to undergo a final endoscopy at the time of withdrawal. Further, an endoscopy could have been performed at any time "for cause" (e.g., if a patient experienced GI symptoms). For calculating ulcer incidences, the denominator was the number of patients undergoing endoscopy at the scheduled time plus the number of patients who were found to have an ulcer at any endoscopy.

6.1.2.1 Studies with Baseline and 12-Week Endoscopy: Studies 021 and 022

The incidence of risk factors for gastroduodenal ulceration such as history of GI bleeding or ulceration, history of cardiovascular disease, positive *H. pylori* serology, or low dose aspirin use (≤325 mg/day) for patients enrolled in Studies 021 and 022 are shown in Table 35. Table 36 shows the baseline endoscopy scores. The distribution of scores was similar across treatment groups. More than 50% of the patients had normal gastric and duodenal mucosa and no patients had an ulcer.

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Table 35. Demographics, Medical History, Baseline *H. pylori* Status, and Aspirin Use: Studies 021 and 022

Study 021	Placebo (N=247)	Celecoxib(BID Dose) 50 mg (N=258)	100 mg (N=240)	200 mg (N=237)	400 mg -	Naproxen 500 mg BID (N=233)
Mean Age	61.1	60.8	61.8	61.2	[redacted]	62.5
% Female	69	65	68	70		68
History of GI Bleeding	9 (4%)	6 (2%)	9 (4%)	3 (1%)		3 (1%)
History of Gastroduodenal Ulcer	48 (19%)	40 (16%)	37 (15%)	36 (15%)		42 (18%)
History of Cardiovascular Disease	161 (65%)	153 (59%)	137 (57%)	137 (58%)		147 (63%)
H. pylori Positive Serology	85 (35%)	103 (41%)	79 (33%)	87 (38%)		87 (39%)
Aspirin Use (≤325 mg/day)	35 (14%)	31 (12%)	32 (13%)	38 (16%)		39 (17%)
Study 022	**(N=231)**	-	**(N=240)**	**(N=235)**	**(N=218)**	**(N=225)**
Mean Age	54.1	[redacted]	54.4	54.7	54.1	54.6
% Female	73		74	73	72	72
History of GI Bleeding	6 (3%)		6 (3%)	4 (2%)	3 (1%)	4 (2%)
History of Gastroduodenal Ulcer	31 (13%)		43 (18%)	38 (16%)	30 (14%)	33 (15%)
History of Cardiovascular Disease	105 (45%)		112 (47%)	104 (44%)	86 (39%)	95 (42%)
H. pylori Positive Serology	78 (34%)		77 (32%)	75 (32%)	50 (23%)	56 (25%)
Aspirin Use (≤325 mg/day)	19 (8%)		24 (10%)	26 (11%)	14 (7%)	19 (8%)

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Table 36. Baseline Endoscopy Scores(a): Studies 021 and 022

Endoscopy Score(b)		Celecoxib(BID Dose)				Naproxen
Study 021	Placebo (N=247)	50 mg (N=258)	100 mg (N=240)	200 mg (N=237)	400 mg -	500 mg BID (N=233)
Gastric						
0 (no visible lesions)	130 (53%)	150 (58%)	145 (60%)	143 (60%)		141 (61%)
1 (1-10 petechiae)	34 (14%)	24 (9%)	30 (13%)	21 (9%)		23 (10%)
2 (>10 petechiae)	5 (2%)	12 (5%)	4 (2%)	12 (5%)		4 (2%)
3 (1-5 erosions)	55 (22%)	58 (22%)	46 (19%)	41 (17%)		54 (23%)
4 (6-10 erosions)	21 (9%)	14 (5%)	15 (6%)	20 (8%)		11 (5%)
5 (11-25 erosions)	2 (<1%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)
Duodenal						
0 (no visible lesions)	208 (84%)	213 (83%)	212 (88%)	207 (87%)		205 (88%)
1 (1-10 petechiae)	12 (5%)	17 (7%)	12 (5%)	19 (8%)		8 (3%)
2 (>10 petechiae)	2 (<1%)	7 (3%)	2 (<1%)	5 (2%)		4 (2%)
3 (1-5 erosions)	24 (10%)	20 (8%)	11 (5%)	6 (3%)		14 (6%)
4 (6-10 erosions)	1 (<1%)	1 (<1%)	3 (1%)	0 (0%)		2 (<1%)
5 (11-25 erosions)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)
Study 022	**(N=231)**	-	**(N=240)**	**(N=235)**	**(N=218)**	**(N=225)**
Gastric						
0 (no visible lesions)	134 (58%)		144 (60%)	136 (58%)	117 (54%)	124 (55%)
1 (1-10 petechiae)	28 (12%)		21 (9%)	33 (14%)	30 (14%)	22 (10%)
2 (>10 petechiae)	2 (<1%)		2 (<1%)	6 (3%)	4 (2%)	7 (3%)
3 (1-5 erosions)	58 (25 %)		59 (25%)	46 (20%)	48 (22%)	53 (24%)
4 (6-10 erosions)	9 (4%)		14 (6%)	13 (6%)	18 (8%)	19 (8%)
5 (11-25 erosions)	0 (0%)		0 (0%)	1 (<1%)	1 (<1%)	0 (0%)
Duodenal						
0 (no visible lesions)	199 (86%)		215 (90%)	200 (85%)	187 (86%)	193 (86%)
1 (1-10 petechiae)	7 (3%)		11 (5%)	12 (5%)	15 (7%)	13 (6%)
2 (>10 petechiae)	3 (1%)		2 (<1%)	4 (2%)	2 (<1%)	2 (<1%)
3 (1-5 erosions)	21 (9%)		11 (5%)	16 (7%)	13 (6%)	13 (6%)
4 (6-10 erosions)	1 (<1%)		1 (<1%)	3 (1%)	1 (<1%)	4 (2%)
5 (11-25 erosions)	0 (0%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)

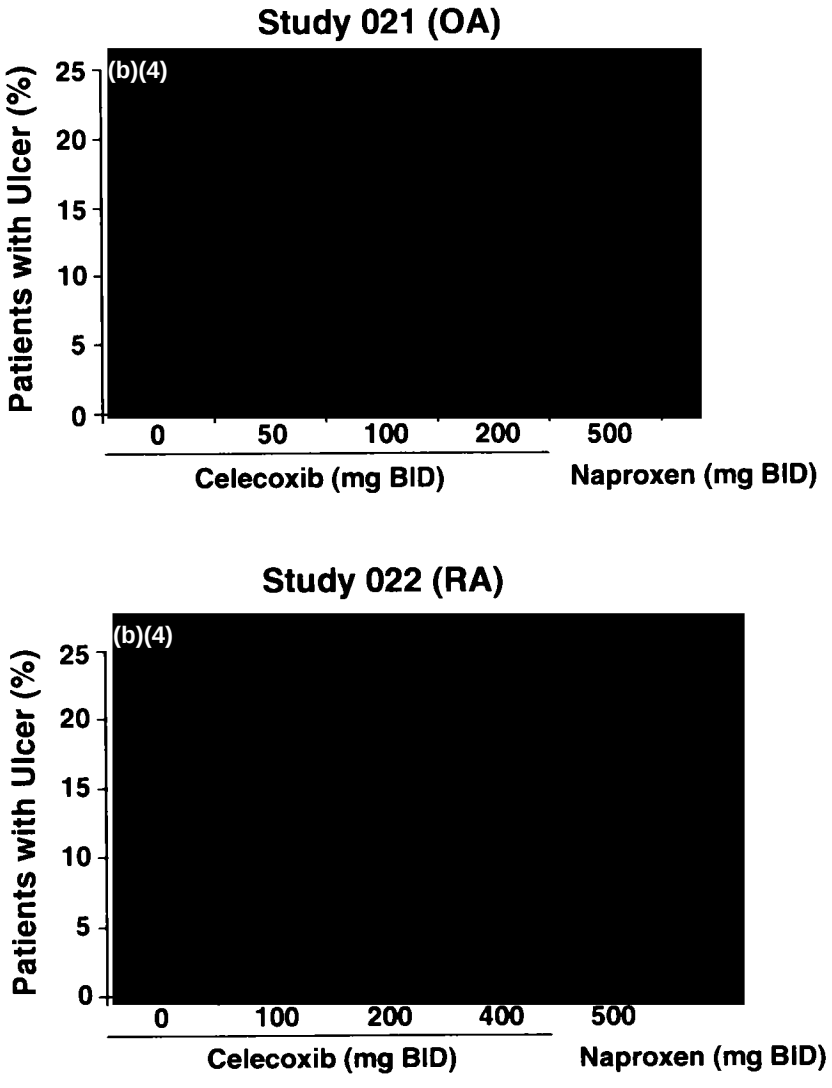
a) Number of patients (%)
b) Endoscopy Scoring Scale ranged from 0 to 7. A score of 6 was >25 erosions and a score of 7 was an ulcer. An erosion was defined as any break in the mucosa without depth. An ulcer was defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth.

Figure 22 shows the gastroduodenal ulceration incidences in Studies 021 and 022. Table 37 summarizes the gastroduodenal results as well as showing the incidences of gastric and duodenal ulcer separately. Over the 12-week treatment period, gastroduodenal ulcer incidences for placebo were consistent between these two studies at 4%. Gastroduodenal ulcer incidences for celecoxib 50 mg BID through 400 mg BID were almost identical among dose groups and similar to placebo. In contrast, incidences of gastroduodenal ulcers over the 12 weeks of these studies for naproxen were markedly higher than those for celecoxib or placebo.

None of the differences in gastroduodenal ulcer incidence between placebo and celecoxib, at any dose, was statistically significant in these two studies, nor were there statistical differences among celecoxib doses. In contrast, all gastroduodenal ulcer

incidences were statistically significantly higher for naproxen than for placebo or celecoxib at all doses. Comparisons of the gastric and duodenal ulcer results separately yielded the same statistical results with the exception that the duodenal ulcer incidences were not statistically significantly different between celecoxib 100 mg (2%) and naproxen (6%) in Study 022.

Figure 22. Gastroduodenal Ulcer Incidences in 12-Week Studies with Baseline and 12-Week Endoscopy: Studies 021 and 022



* Significantly different from all other treatments; p<0.001.

Table 37. Ulcer Incidences: Studies 021 and 022

Study	Placebo	Celecoxib 50 mg BID	Celecoxib 100 mg BID	Celecoxib 200 mg BID	Celecoxib 400 mg BID	Naproxen 500 mg BID
Gastroduodenal						
021	4 (4/106)	5 (8/164)	5 (7/155)	9 (13/150)	-	23 (34/146)*
022	4 (4/99)	-	6 (9/148)	4 (6/145)	6 (8/130)	26 (36/137)*
Gastric						
021	4 (4/106)	5 (8/164)	5 (7/155)	7 (10/148)	-	18 (25/141)*
022	3 (3/99)	-	4 (6/147)	3 (4/144)	5 (7/130)	22 (29/134)*
Duodenal						
021	0 (0/104)	0 (0/158)	0 (0/151)	2 (3/148)	-	8 (11/140)*
022	1 (1/97)	-	2 (3/147)	1 (2/144)	<1 (1/129)	6 (8/128)**

* Significantly different from all other treatments; p<0.05.
** Significantly different from placebo and celecoxib 200 and 400 mg BID; p<0.05.
Entries are % of patients with ulcer (No. with ulcer/ No. with known result). Known endoscopy results include an ulcer detected at any time, or a finding of no ulcer at an endoscopy performed at 84 ±7 days.

6.1.2.2 24-Week Endoscopy Study: Study 041

In Study 041, patients with RA were treated with celecoxib 200 mg BID or diclofenac SR 75 mg BID for 24 weeks. Four hundred thirty patients (approximately 66% of the total enrolled) underwent UGI endoscopy at the final visit. Demographics, relevant medical history, and the incidence of positive *H. pylori* serology are shown in Table 38.

Table 38. Demographics, Medical History, and *H. pylori* Status(a): Study 041

	Celecoxib 200 mg BID (N=326)	Diclofenac SR 75 mg BID (N=329)
Mean Age	55.9	54.5
% Female	76	71
History of GI Bleeding	4 (1%)	1 (<1%)
History of Gastroduodenal Ulcer	28 (9%)	27 (8%)
History of Cardiovascular Disease	83 (25%)	78 (24%)
H. pylori Positive Serology	122 (37%)	124 (38%)
Aspirin Use (≤325 mg/day)	5 (1.5%)	5 (1.5%)

a) Determined at time of endoscopy; N=212 for celecoxib and N=218 for diclofenac SR

Figure 23 shows the gastroduodenal ulceration incidences in this study, and Table 39 shows the gastroduodenal, gastric, and duodenal ulcer incidences. All ulcer incidences were statistically significantly lower for celecoxib than for diclofenac. The 4% gastroduodenal ulcer incidence for celecoxib 200 mg BID was similar to that observed for the same celecoxib dose in the 12-Week studies (Studies 021 and 022) and to the placebo incidence seen in those studies. The 15% incidence for diclofenac was consistent with results of previous endoscopy studies involving diclofenac. (2,25) The differences

in ulcer incidences between the two treatment groups were statistically significant in all three comparisons of gastroduodenal ulcers, gastric ulcers, and duodenal ulcers.

Figure 23. Gastroduodenal Ulcer Incidences in the 24-Week Endoscopy Study: Study 041

* Significantly different from celecoxib; p<0.001.

Table 39. Ulcer Incidences: Study 041

Endoscopy Result	Celecoxib 200 mg BID	Diclofenac SR 75 mg BID
Gastroduodenal	4 (8/212) *	15 (33/218)
Gastric	2 (5/212) *	11 (24/218)
Duodenal	2 (4/212) *	7 (15/217)

* Significantly different from diclofenac; p<0.05.
Entries are % of patients with ulcer (No. of patients with ulcer/total patients).

6.1.2.3 Serial Endoscopy Studies; Studies 062 and 071

Demographics, relevant medical history, and the incidence of positive *H. pylori* serology or low dose aspirin use for the serial endoscopy studies (Studies 062 and 071) are shown in Table 40. Table 41 shows the baseline endoscopy scores. The distribution of scores was similar across treatment groups. More than 50% of the patients had normal gastric and duodenal mucosa.

The gastroduodenal ulceration incidences within each interval (i.e., 0-4 weeks, 4-8 weeks, and 8-12 weeks) for the two 12-week serial endoscopy studies are shown in Figure 24. When an ulcer was detected, the patient was withdrawn from the study. Therefore, only patients who did not have an ulcer in a previous interval are included in the subsequent 4-week intervals in this analysis. As Figure 24 shows, in both of these studies, the highest incidence of ulceration occurred in the first four weeks of treatment. The ulcer incidences for celecoxib were 4% in the first month, and 2% in both of the remaining two 4 week intervals.

Table 40. Demographics, Medical History, Baseline *H. pylori* Status, and Aspirin Use: Studies 062 and 071

Study 062	Celecoxib 200 mg BID (N=270)(a)	Naproxen 500 mg BID (N=267)	Diclofenac 75 mg BID -	Ibuprofen 800 mg TID -
Mean Age	56.7	57.7		
% Female	67	67		
History of GI Bleeding	10 (4%)	14 (5%)		
History of Gastroduodenal Ulcer	57 (21%	53 (20%)		
History of Cardiovascular Disease	151 (56%)	133 (50%)		
H. Pylori Positive Serology	90 (33%)	88 (33%)		
Aspirin Use (≤325 mg/day)	38 (11%)	32 (12%)		
Study 071	**(N=366)(a)**	-	**(N=387)**	**(N=346)(a)**
Mean Age	57.2		57.2	57.6
% Female	70		67	66
History of GI Bleeding	7 (2%)		6 (2%)	5 (1%)
History of Gastroduodenal Ulcer	39 (11%)		48 (12%)	41 (12%)
History of Cardiovascular Disease	161 (44%)		153 (40%)	151 (44%)
H. pylori Positive Serology	119 (33%)		112 (29%)	110 (32%)
Aspirin Use (≤325 mg/day)	48 (13%)		44 (11%)	41 (12%)

a) Includes one patient who was randomized but did not receive study medication and was not included in the ITT cohort.

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Table 41. Baseline Endoscopy Scores(a): Studies 062 and 071

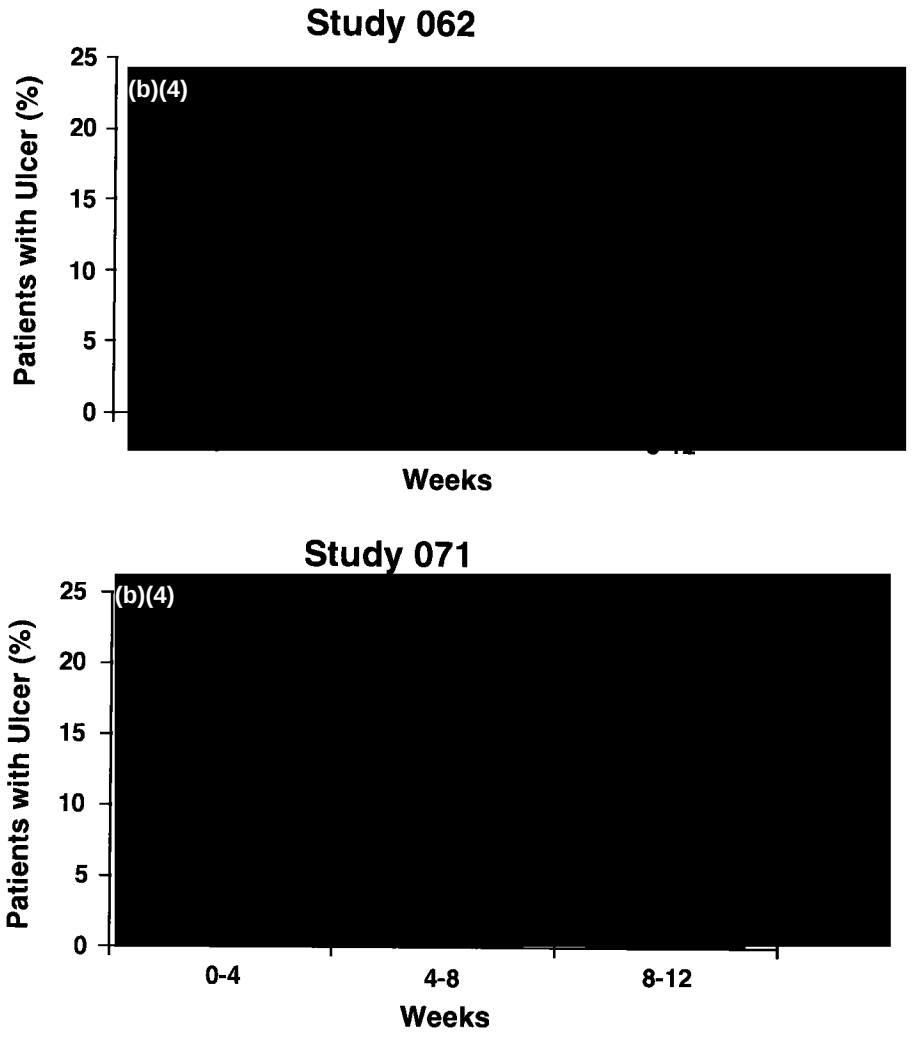
Endoscopy Score(b) Study 062	Celecoxib 200 mg BID (N=270)(c)	Naproxen 500 mg BID (N=267)	Diclofenac 75 mg BID -	Ibuprofen 800 mg TID -
Gastric				
0 (no visible lesions)	161 (60%)	159 (60%)		
1 (1-10 petechiae)	29 (11%)	29 (11%)		
2 (>10 petechiae)	8 (3%)	5 (2%)		
3 (1-5 erosions)	52 (19%)	56 (21%)		
4 (6-10 erosions)	16 (6%)	11 (4%)		
5 (11-25 erosions)	3 (1%)	4 (1%)		
6 (>25 erosions)	1 (<1%)	2 (<1%)		
Ulcer	0 (0%)	1 (<1%)		
Duodenal				
0 (no visible lesions)	229 (85%)	235 (88%)		
1 (1-10 petechiae)	19 (7%)	15 (6%)		
2 (>10 petechiae)	3 (1%)	4 (1%)		
3 (1-5 erosions)	17 (6%)	11 (4%)		
4 (6-10 erosions)	1 (<1%)	2 (<1%)		
5 (11-25 erosions)	1 (<1%)	0 (0%)		
Study 071	**(N=366)(b)**	-	**(N=387)**	**(N=346)(b)**
Gastric				
0 (no visible lesions)	205 (56%)		240 (62%)	205 (59%)
1 (1-10 petechiae)	30 (8%)		41 (11%)	38 (11%)
2 (>10 petechiae)	11 (3%)		7 (2%)	9 (3%)
3 (1-5 erosions)	87 (24%)		71 (18%)	66 (19%)
4 (6-10 erosions)	19 (5%)		16 (4%)	16 (5%)
5 (11-25 erosions)	10 (3%)		9 (2%)	9 (3%)
6 (>25 erosions)	4 (1%)		3 (<1%)	2 (<1%)
Duodenal				
0 (no visible lesions)	297 (81%)		330 (85%)	292 (85%)
1 (1-10 petechiae)	30 (8%)		22 (6%)	20 (6%)
2 (>10 petechiae)	4 (1%)		5 (1%)	7 (2%)
3 (1-5 erosions)	30 (8%)		26 (7%)	23 (7%)
4 (6-10 erosions)	3 (<1%)		4 (1%)	2 (<1%)
5 (11-25 erosions)	2 (<1%)		0 (0%)	1 (<1%)

a) No. of Patients (%)
b) Endoscopy Scoring Scale ranged from 0 to 7. A score of 7 was an ulcer. An erosion was defined as any break in the mucosa without depth. An ulcer was defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth.
c) Includes one patient who was randomized but did not receive study medication and was not included in the ITT cohort.

Table 40 summarizes the gastroduodenal, gastric and duodenal ulcer data. The incidences in the table are cumulative, meaning that an ulcer found at any endoscopy is counted for all subsequent assessments. Therefore, the incidences shown in the rows labeled "0-12 wk" in the table represent all ulcers identified at any time in the study. It is not unexpected that the ulcer incidences were higher than in the other endoscopy studies. Any given patient could have undergone three post-Baseline endoscopies, each of which contributed to the probability of finding an ulcer. The other studies (Studies 021, 022, and 041) only afforded one opportunity to identify an ulcer in a given patient.

In Studies 062 and 071, all differences in incidence of ulceration were statistically significant between celecoxib and both naproxen and ibuprofen at all time points for gastroduodenal, gastric, and duodenal ulcers. Differences between celecoxib and diclofenac did not achieve statistical significance except in the incidence of duodenal ulcers.

Figure 24. **Gastroduodenal Ulcer Incidences in 12-Week Studies with Serial Endoscopies: Studies 062 and 071**



* Significantly different from celecoxib; p ≤0.05.
* * Significantly different from diclofenac; p <0.002.

Table 42. Cumulative Ulcer Incidences: Studies 062 and 071

Study	Celecoxib 200 mg BID	Naproxen 500 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Gastroduodenal				
062				
0-4 wk	4 (10/252) *	19 (47/247)		
0-8 wk	6 (15/237) *	32 (73/229)		
0-12 wk	9 (18/211) *	41 (87/214)		
071				
0-4 wk	4 (13/337) †		5 (18/350) †	13 (42/323)
0-8 wk	6 (20/309) †		9 (28/324) †	20 (57/283)
0-12 wk	9 (25/294) †		12 (36/306) †	28 (78/276)
Gastric				
062				
0-4 wk	3 (7/250) *	16 (39/245)		
0-8 wk	4 (9/234) *	28 (61/221)		
0-12 wk	6 (12/205) *	37 (74/202)		
071				
0-4 wk	4 (12/337) †		4 (14/350) †	9 (29/323)
0-8 wk	6 (18/308) †		7 (22/321) †	15 (40/270)
0-12 wk	8 (23/293) †		9 (27/301) †	23 (60/259)
Duodenal				
062				
0-4 wk	2 (4/251) *	5 (13/247)		
0-8 wk	3 (7/231) *	9 (18/194)		
0-12 wk	4 (8/203) *	12 (19/158)		
071				
0-4 wk	<1 (1/337) †‡		2 (8/350)	5 (16/321)
0-12 wk	<1 (2/296) †‡		3 (10/313) †	8 (20/256)
0-12 wk	1 (3/275) †‡		5 (14/287)	9 (22/238)

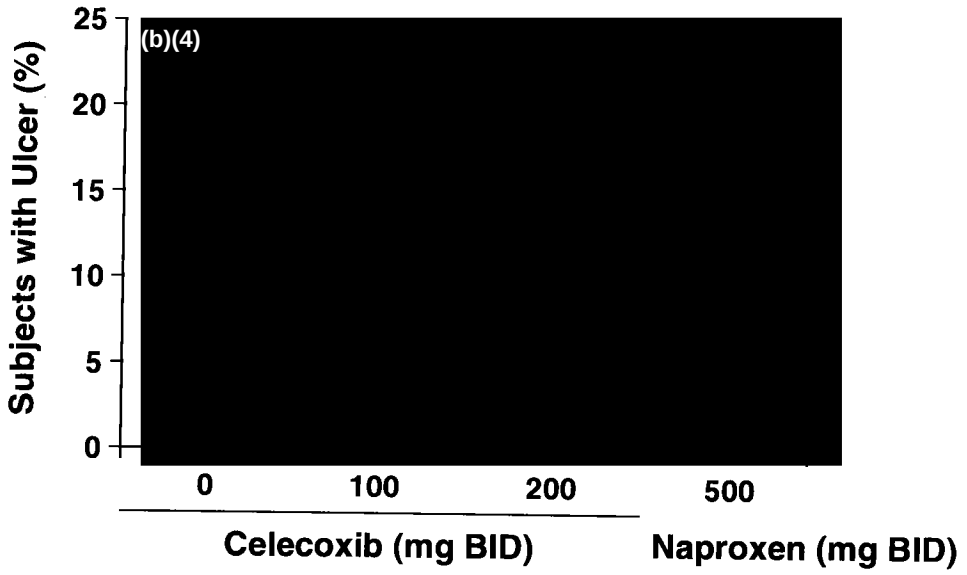
* Significantly different from naproxen; $p<0.05$.
† Significantly different from ibuprofen; $p<0.05$.
‡ Significantly different from diclofenac; $p<0.05$.
Entries are % of patients with ulcer (No. with ulcer/total no. with known result). Known endoscopy results include an ulcer detected at any time, or a finding of no ulcer at an endoscopy performed at the scheduled visit ±7 days.

6.1.3 7-Day Endoscopy Study

Study 014 was a randomized, double-blind study conducted in healthy volunteers with normal gastroduodenal mucosa at baseline endoscopy. Treatment groups included placebo, celecoxib 100 mg BID, celecoxib 200 mg BID, and naproxen 500 mg BID.

None of the 32 subjects receiving placebo, or the 64 subjects receiving celecoxib, developed an ulcer; in contrast, six of the 32 subjects receiving naproxen developed a gastric ulcer (Figure 25).

Figure 25. Ulcer Incidences at Day 7: Study 014



* Significantly different from other treatments; $p<0.05$.

6.1.4 Clinically Significant UGI Events

An independent GI Consultants Committee consisting of three gastroenterologists was established to review, in a blinded fashion, case summaries of potential clinically significant UGI events that occurred during the conduct of clinical trials. This monitoring system included the 14 controlled arthritis trials (Studies 012, 013, 020, 021, 022, 023, 041, 042, 047, 054, 060, 062, 071, and 087) and the North American Long-term Open Label Arthritis Study (Study 024).

Investigators were instructed to report any event considered to represent a potentially clinically significant UGI event (e.g., UGI bleeding, perforation, or gastric outlet obstruction). Data pertaining to the event were summarized and distributed to each of the Committee members who reviewed each case and determined by consensus if the event was a clinically significant UGI event. Committee members were blinded to which treatment patients had received and in which study the patient was enrolled.

The definitions of clinically significant UGI events were based in large part on the design and results of a large prospective study on incidences of clinically significant UGI events caused by NSAIDs. (26)

The committee adjudicated all potentially clinically significant UGI events according to the following prospectively defined criteria:

1. UGI Bleeding
    a. hematemesis with a lesion* at endoscopy or x-ray,
    b. lesion at endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer),
    c. melena with a lesion at endoscopy or x-ray,
    d. hemoccult positive stools with a lesion at endoscopy or x-ray with evidence of serious bleeding, which included:
        (1) fall in hematocrit over 5% (absolute change)
        (2) signs of postural vital sign changes (increase of pulse rate of 30 bpm and a decrease in systolic blood pressure of 20 mm Hg and a diastolic blood pressure of 10 mm Hg)
        (3) transfusion of more than two units of blood
        (4) blood in the stomach

* A lesion is an ulcer or large erosion.

2. Perforation

This was defined as a perforated lesion that required surgery. It could involve a laparoscopic repair, but only if evidence of the perforation were unequivocal such as free air in the abdomen visible by x-ray, or peritoneal signs upon physical examination.

3. Gastric Outlet Obstruction

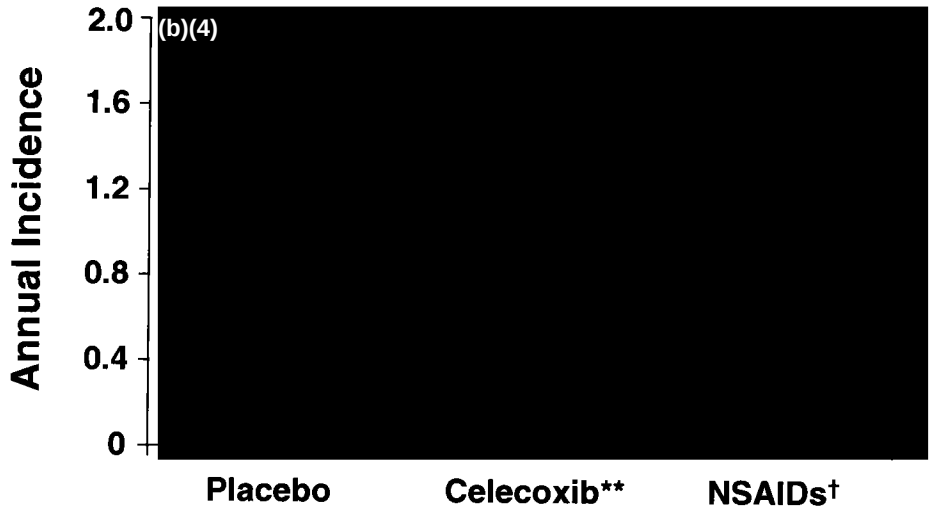
Gastric outlet obstruction was required to be diagnosed by the Investigator, and the diagnosis had to be supported by endoscopy (e.g., a tight edematous ulcer in the pyloric channel) or by x-ray results (e.g., a dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with ulcer in the channel or severe narrowing and edema).

When lower GI adverse events including small bowel or colonic obstruction, ulceration, bleeding, perforation, stricture, colitis were reported by investigators, the cases were reviewed by the committee.

6.1.4.1 Controlled Arthritis Trials

A total of 101 cases were referred to the Committee for adjudication. Eleven of these met the criteria for clinically significant UGI events. The annual incidence of clinically significant UGI events for placebo, celecoxib and NSAIDs are shown in Figure 26 and Table 43. The rate of development of these events per patient-year was approximately eight-fold lower for celecoxib (0.20%) than for NSAIDs (1.68%). The difference (1.48%) in the annual incidence of clinically significant UGI events between celecoxib and NSAIDs was statistically significant (95% confidence interval 0.35% to 2.62%).

Figure 26. Annual Incidence of Clinically Significant UGI Adverse Events: Controlled Arthritis Trials



* Significantly different from celecoxib; P <0.05 (1.48%; 95% confidence interval 0.35% - 2.62%)
** Fourteen controlled arthritis trials: Celecoxib 25-400 mg BID
† Naproxen 500 mg BID; Diclofenac 50-75 mg BID; and Ibuprofen 800 mg TID

The nine clinically significant UGI events that occurred with NSAIDs included five events over 236 patient-years of exposure for naproxen (annual incidence 2.1%), three events over 237 patient-years of exposure for diclofenac (annual incidence 1.3%) and one event over 62 patient-years of exposure for ibuprofen (annual incidence 1.6%). Of these nine cases, seven were UGI bleeding episodes and two were gastric outlet obstructions (both occurring in patients receiving naproxen). The two clinically significant UGI events that were associated with 1020 patient-years of exposure with

celecoxib were UGI bleeding episodes. One of these events occurred in a patient taking celecoxib 100 mg BID and the other in a patient taking celecoxib 200 mg BID.

Table 43. Annual Incidence of Clinically Significant UGI Events: Controlled Arthritis Trials

	Placebo	Celecoxib	NSAIDs
No. of events	0	2	9
Patient-years of exposure	208	1020	535
Annual Incidence	**0%**	**0.20%**	**1.68%***

* Significantly different from celecoxib; p<0.05

6.1.4.2 Long-Term Open-Label Arthritis Study

In the long-term open-label trial, 69 possibly clinically significant UGI events were referred to the Committee for evaluation. Seven cases met the criteria for clinically significant UGI events. The annual incidence of clinically significant UGI events of 0.26% with celecoxib in the long-term open-label arthritis study (Table 44) is consistent with an annual incidence of 0.20% seen in the controlled arthritis trials. Furthermore, as shown in Table 44, with increased patient exposure to celecoxib in this study, the annual incidence of clinically significant UGI events has fallen to 0.18%.

Table 44. Annual Incidence of Clinically Significant UGI Events: North American Long-Term Open-Label Arthritis Study

	Through 11/21/97(a)	Through 7/24/98(b)
No. of events	7	9
Patient-years of exposure	2672	5002
Annual Incidence	**0.26%**	**0.18%**

a) NDA Submission
b) 120-day Safety Update

6.1.5 Conclusions

Based on the results of replicate endoscopy trials and a monitoring program for clinically significant UGI events, it is concluded that:

- The incidences of gastroduodenal, gastric, and duodenal ulceration with celecoxib at therapeutic and supratherapeutic doses was statistically significantly lower than that of NSAIDs and similar to placebo.
- Celecoxib was associated with an eight-fold lower risk of clinically significant UGI events than NSAIDs, and the annual incidence with celecoxib was similar to that with placebo.

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